CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-229

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-229

Code: 2&3 S

Trade Name: Prilosec® 1 Tablets, 20 mg

Stamp Date: 4/11/2000

Active Ingredient: Omeprazole Magnesium

Related INDs: I 54,307

Sponsor: AstraZeneca Pharmaceuticals

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Related NDA: N 19-810

Type of Submission: Switch from Prescription to OTC

Synopsis

Omeprazole is a potent inhibitor of gastric acid secretion. It currently is being marketed for the treatment of a variety of short- and long- term GI conditions.
The sponsor submitted NDA 21-229 to gain approval for over-the-counter (OTC) marketing of omeprazole magnesium tablets for the treatment and prevention of heartburn under the proposed market name "Prilosec 1".

The Clinical Pharmacology and Biopharmaceutics section of the NDA consisted of studies on the pharmacokinetics/pharmacodynamics of omeprazole, metabolic drug-drug interactions, and relative bioavailability of the omeprazole magnesium tablets (Prilosec 1®) and the currently marketed Prilosec® prescription capsules. A complete listing of the Clinical Pharmacology and Biopharmaceutics-related studies submitted to this NDA is included in Appendix 1.

The sponsor has adequately characterized the relevant clinical pharmacology and biopharmaceutics-related aspects of the drug. ——— is highly bound to plasma proteins (95%). It is extensively metabolized by hepatic CYP-450 isozymes, primarily CYP 2C19 and CYP 3A4, to hydroxy and sulphone metabolites. The plasma elimination half-life is less than an hour with no intact drug detected in feces and urine indicating complete metabolism. Dosage adjustment is warranted for omeprazole in some Asian as well as hepatic imapirment patients. The bioavailability of a 20 mg single dose is 40% and increases to 60% at steady state, indicating that omeprazole exhibits time-dependent pharmacokinetics. The bioavailability of omeprazole tablets is significantly affected by food intake.

The To-Be-Marketed (TBM) omeprazole tablets were shown to be similar, but not bioequivalent, to the marketed prescription capsules. However, additional PK and clinical studies were submitted to the current application in support of the safety and efficacy of omeprazole magnesium tablets.

Significant metabolic drug-drug interactions were demonstrated for omeprazole with diazepam and clarithromycin.

Recommendations:

The Human Pharmacokinetics and Bioavailability section of NDA 21-229 submitted on 12/6/1999 is acceptable from the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics. OCPB-related labeling language will be addressed at the appropriate time.

[/S/] 11/13/00

Suliman I. Al-Fayoumi, Ph.D.
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Division of Pharmaceutical Evaluation II

Suresh Doddapaneni, Ph.D., Team leader [/S/] 11/13/00

cc: HFD-180: NDA 21-229 (1x); DIV FILE (1x); MWALSH (1x); SDODDAPANENI (1x); SALFAYOUMI (1x); HFD-870 HMALINOWSKI (1x); CDR: ATTN Zom Zadeng

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1. What is the pharmacological class, scientific rationale and intended use of Prilosec 1 (omeprazole magnesium)?

Omeprazole, the first proton pump inhibitor approved for prescription use for a variety of gastric acid-related diseases, is being sought for OTC marketing as the sponsor claims it results in a longer duration of heartburn relief compared to H_2-blockers currently on the OTC market.

Omeprazole is a specific inhibitor of the proton pumps in the parietal cells of the stomach, and hence, it is a potent inhibitor of gastric acid secretion. Omeprazole has been approved for marketing in the US since 1989 for several conditions including, short-term treatment of duodenal ulcer (DU) and gastric ulcer (GU), healing and maintenance of healing of erosive esophagitis, long-term management of pathologic hypersecretory conditions, treatment of heartburn and other symptoms associated with GERD, in combination with clarithromycin for short-term treatment of patients with *helicobacter pylori* infection and DU to reduce the risk of DU recurrence, and in combination with clarithromycin and amoxicillin for short-term treatment of patients with *helicobacter pylori* infection and DU.

The sponsor is seeking approval for marketing omeprazole, 20 mg O.D. as the magnesium salt (Prilosec 1®) in the over-the-counter (OTC) setting for: 1) Relief of heartburn, acid indigestion and sour stomach, and 2) Prevention of heartburn, acid indigestion and sour stomach brought on by consuming food and beverages or associated with events such as stress, hectic lifestyle, lying down or exercise. It should be noted that the proposed indications for OTC marketing are new indications of omeprazole.

The sponsor claims that consumer surveys show that a significant portion of OTC heartburn sufferers are dissatisfied with current products, primarily due to inadequate duration of relief. Thus, once a day dosing with up to 24 hr duration of prevention or relief would be beneficial for those consumers.

An advisory committee (AC) meeting took place on 10/20/00 to discuss approvability of omeprazole 20 mg in the OTC setting for the sponsor's proposed indications. The draft minutes of the meeting indicate that the AC members did vote down the approvability of the product in the OTC setting for the proposed indications.

2. How does the currently marketed capsule formulation compare relative to the To-be-Marketed (TBM) tablet formulation?

Prilosec 1® tablet and Prilosec® capsule formulations are similar on their relative bioavailabilities. In addition, the safety and efficacy of Prilosec 1® tablets is supported by several PK and clinical studies.

Omeprazole is currently available for prescription indications as delayed-release, acid-resistant pellets dispensed in hard gelatin capsules. The dosage form proposed by the sponsor for OTC indications is a Multiple Unit Pellet System (MUPS) tablet dosage form

consisting of acid resistant pellets of the omeprazole magnesium salt (0.6 mg magnesium for a 20 mg omeprazole magnesium dose).

A study was conducted to evaluate the relative bioavailability of the proposed omeprazole 2 X 10 mg tablets and 20 mg tablets to the currently marketed 20 mg Prilosec® capsules (Protocol 200). It should be noted that the 20 mg tablet is the only formulation currently proposed by the sponsor for OTC marketing. The study was an open-label, single-dose, three-way, cross-over study.

The results indicate that 2 X 10 mg tablets are bioequivalent to 20 mg tablets and hence, interchangeable. However, both the confidence intervals for the 20 mg tablets and 10 mg tablets fell outside the acceptable goalposts for bioequivalence to the marketed capsules on C_{max} (80-125%) (Table 1, Fig. 1).

The study shows that the proposed MUPS tablet and marketed capsule formulations are similar on their relative bioavailabilities. The C_{max} value was 30% higher for the tablet relative to the marketed capsule. Despite the two dosage forms not being bioequivalent, the tablet was adequately characterized from a CPB perspective. Food effect (study OME-0008) as well as multiple dose (Study OME 0009) studies are included in the submission. In addition, 6 clinical studies were submitted to the current application in support of the safety and efficacy of omeprazole 20 mg MUPS tablets.

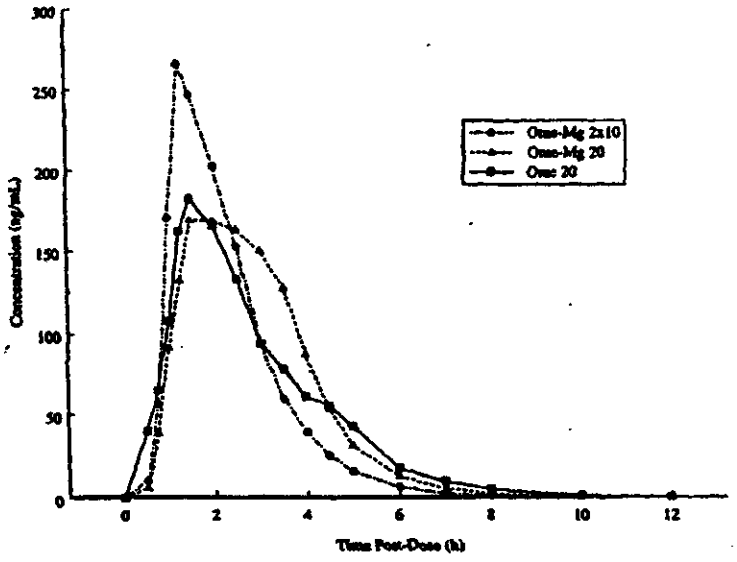


Fig. 1. Mean omeprazole plasma levels following administration of omeprazole 2 X 10 mg tablets, one omeprazole 20 mg tablet and one omeprazole 20 mg capsule.

Table 1. Ratios of geometric means for omeprazole AUC and C_{max} estimates (n =28)

	C_{max} ratio	AUC ratio
20 mg tablet/20 mg capsule	1.289 (1.102-1.507)*	1.042 (0.980-1.108)
2 X 10 mg tablet/20 mg tablet	1.010 (0.863-1.181)	0.960 (0.903-1.021)
2 X 10 mg tablet/20 mg capsule	1.301 (1.113-1.522)	1.001 (0.941-1.064)

* 95% Confidence Interval

A complete listing of studies submitted to the Clinical Pharmacology and Biopharmaceutics section of NDA 21-229 are included in appendix 1.

3. Is there a pharmacokinetic/pharmacodynamic relationship for omeprazole with respect to gastric acid suppression activity?

Omeprazole suppresses gastric acid secretion in a dose-dependent manner at 20-80 mg single doses with an increased effect upon repeated daily dosing. While omeprazole has a prolonged duration of action relative to H_2 blockers, it has a delayed onset of action (up to 5 hours). Prilosec 1® tablets and Prilosec® capsules were shown to be similar with respect to suppression of gastric acid in GERD patients.

Omeprazole *per se* is devoid of antisecretory activity. However, under the highly acidic conditions found in the parietal cells of the stomach, it is converted to the active inhibitor, a protonated sulfanilamide, which binds covalently to the gastric proton pump and inhibits it.

Omeprazole has been shown to suppress gastric acid secretion stimulated by pentagastrin, peptone and betazole in a dose-dependent manner at 20-80 mg single doses with an increased effect upon repeated daily dosing, which is likely related to the cumulative effect of omeprazole on the inhibition of gastric acid secretion (Fig. 2). The maximal inhibitory effect on pentagastrin stimulated acid secretion was 65% when measured 24 hrs after administration of repeated once daily doses greater than 20 mg (Fig. 4).

No correlation has been shown between omeprazole plasma concentration and the degree of acid inhibition. However, an apparent relationship was observed between AUC for omeprazole in plasma and the degree of acid suppression.

The results of two studies (Studies 129 & 131) in patients with a history of heartburn who received single oral doses of omeprazole showed that at doses of up to 20 mg, omeprazole was not effective in increasing intragastric pH at 1 hr post-dose.

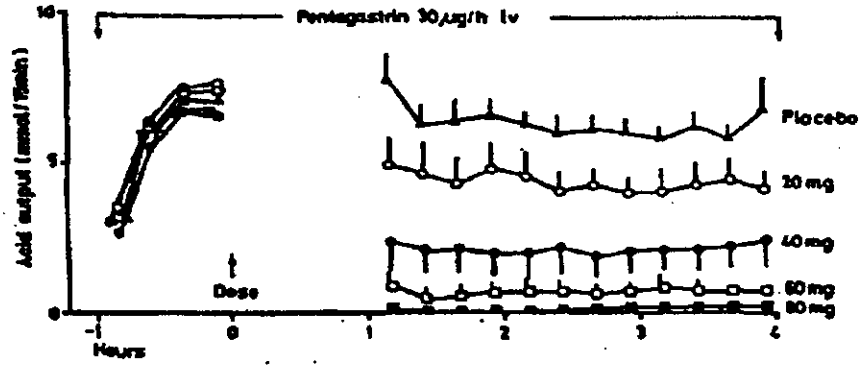


Fig. 2. Effect of oral omeprazole on pentagastrin induced acid secretion in 6 healthy Subjects (Lind et al., 1983).

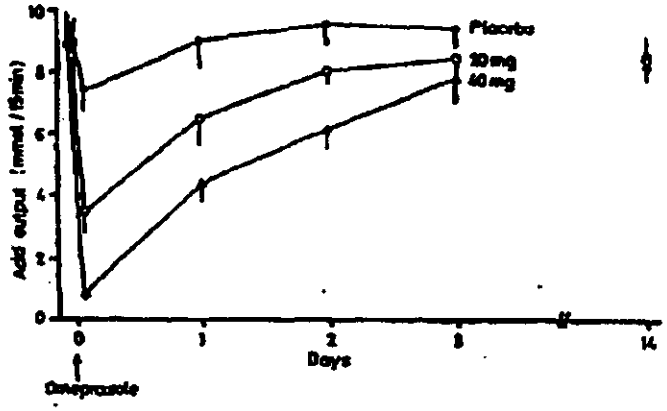


Fig. 3. Duration of action of two different single oral doses of omeprazole in 6 healthy subjects (Lind et al., 1983).

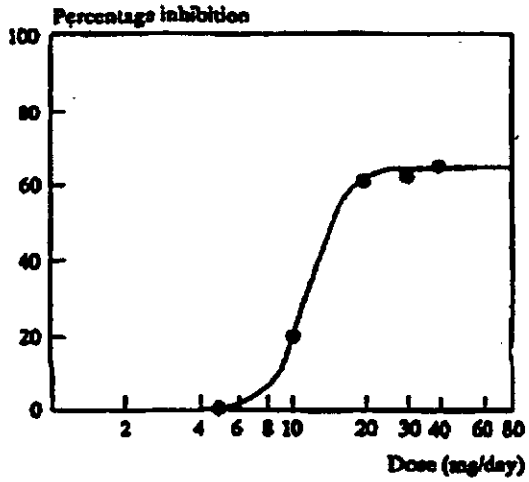


Fig. 4. Dose-response curve for repeated once daily treatments with omeprazole (Lind et at, 1986).

Study 129 was an open-label, single center, famotidine-controlled, single dose crossover study to evaluate the effects of omeprazole on acid suppression in heartburn patients by measuring intragastric and intra-esophageal pH. The pharmacodynamic variables assessed during the study included: intragastric pH at 1 hr post-dose, intragastric pH over 5 hrs post-dose and % time intra-esophageal pH < 4. The results showed that a single dose of famotidine 10 mg raises intragastric pH higher than a single dose of either omeprazole 10 mg or omeprazole 20 mg at 1 hr post-dose and over the first 5 hrs post-dose. Additionally, famotidine 10 mg raises intragastric pH to greater than 4 more quickly than a single dose of either 10 mg or 20 mg omeprazole (Fig. 5 & 6).

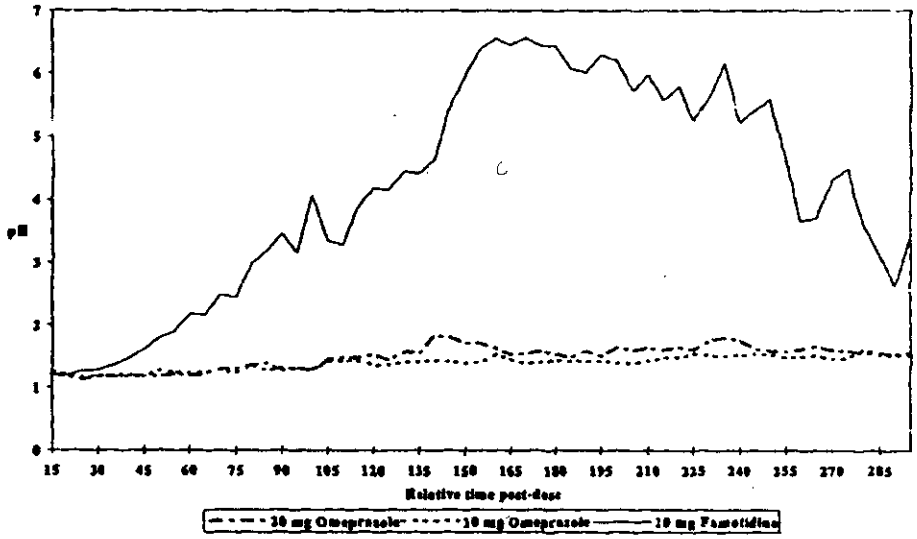
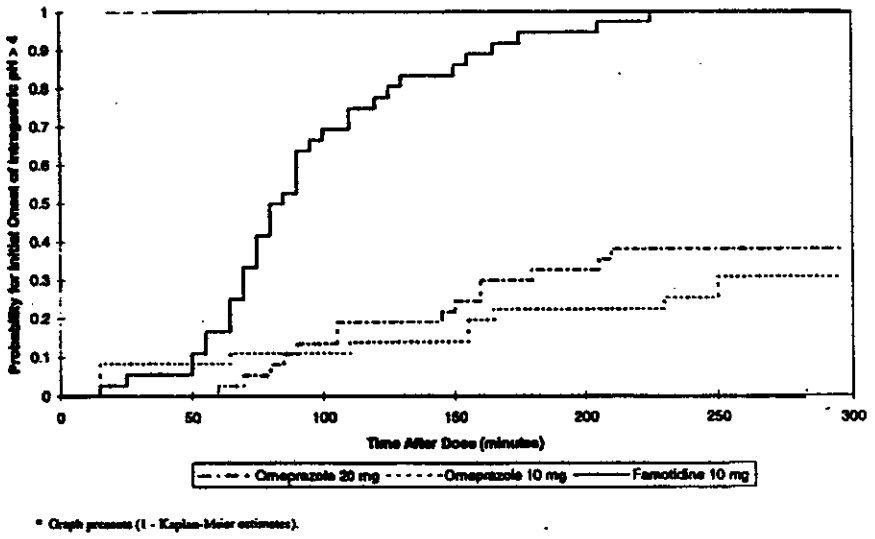


Fig. 5. Median 5 min intragastric pH values postdose by treatment



* Graph presents (1 - Kaplan-Meier estimates).

Fig. 6. Kaplan-Meier estimates for the time to onset of intragastric pH > 4 by treatment

The study design for study 131 was quite similar to that of study 129. The main objective of study 131 was to evaluate the effects of omeprazole on acid suppression. Omeprazole 5, 10 and 20 mg doses were compared vs. placebo on several pharmacodynamic parameters including: mean intragastric pH, intragastric pH at 1 hr post-dose, intragastric pH over 5 hrs post-dose and % time intra-esophageal pH < 4.

The results indicated that a single dose of omeprazole 5, 10 or 20 mg does not significantly increase intragastric pH at 1 hr post-dose, nor does it significantly decrease % time intra-esophageal pH < 4 during 5 hrs post-dose. Only a single dose of omperazole 20 mg increased intragastric pH during 5 hrs post-dose, while omeprazole 10 mg increased the number of patients who reached an intragastric pH > 4 (Fig 7 & 8).

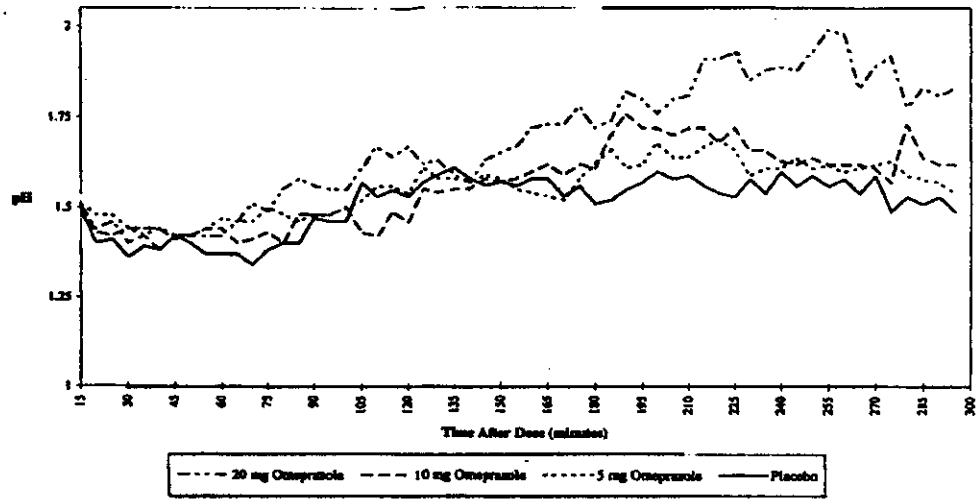
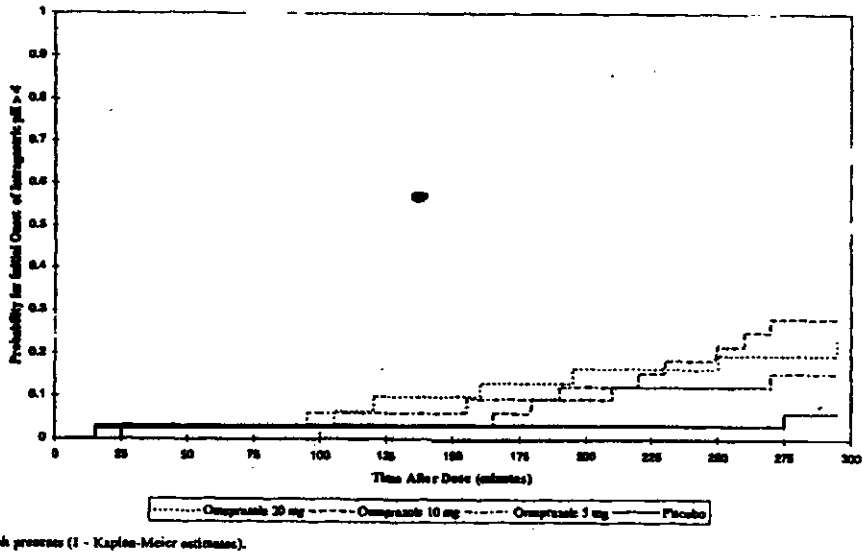


Fig. 7. Median 5 min intragastric pH values postdose by treatment



* Graph presents (1 - Kaplan-Meier estimates).

Fig. 8. Kaplan-Meier estimates for the time to onset of intragastric pH > 4 by treatment

In study SH-OME-0009, omeprazole 20 mg was administered as a new MUPS tablet and the commercially available capsule to patients with symptomatic GERD (n = 36) in an open, randomized, steady-state, cross-over fashion. Intragastric pH was determined over 24 hrs prior to study start and at the end of each of the two treatment periods. In addition, blood samples were collected for determination of omeprazole in plasma.

The study results showed that whereas the ratios of AUC and C_{max} values of tablet/capsule were 0.84 and 0.71, respectively, the ratio of % time intragastric pH $\geq$ 4 for tablet/capsule was 0.99. This indicates that a 30% higher C_{max} and 15% higher AUC of the tablet relative to the capsule did not seem to translate into pharmacodynamic differences (Fig. 9).

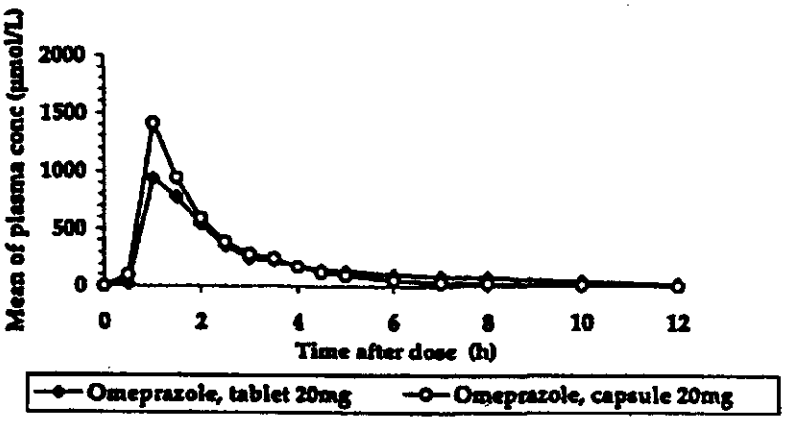


Fig. 9. Mean plasma levels after dosing to steady state of omeprazole as MUPS tablets and capsules.

4. Is there a need for dosage adjustment?

4.1. Food Effect

Food significantly affects the bioavailability of Prilosec 1® 20 mg MUPS tablets. Thus, it should be administered one hour before meals.

A study was conducted to assess the effect of food on the bioavailability of the 20 mg MUPS tablet (Study SH-OME-0008). Single omeprazole 20 mg doses were administered as either prescription capsules (Losec®-Marketed formulation in Europe) or MUPS tablets in an open, randomized, three-way cross-over trial (n = 18). MUPS tablets were given under fasting conditions and after food, while prescription capsules were given only after food.

The estimated treatment ratios on AUC and C_{max} for tablet (food)/tablet (fasting) indicate that AUC increases by 20%, while C_{max} decreases by 34% after food intake relative to the fasting state (Table 2, Fig. 10).

In conclusion, food significantly affects the bioavailability of omeprazole 20 mg MUPS tablets. Prilosec 1® 20 mg MUPS tablets should be administered one

hour before food intake since it was administered as such during the clinical trials.

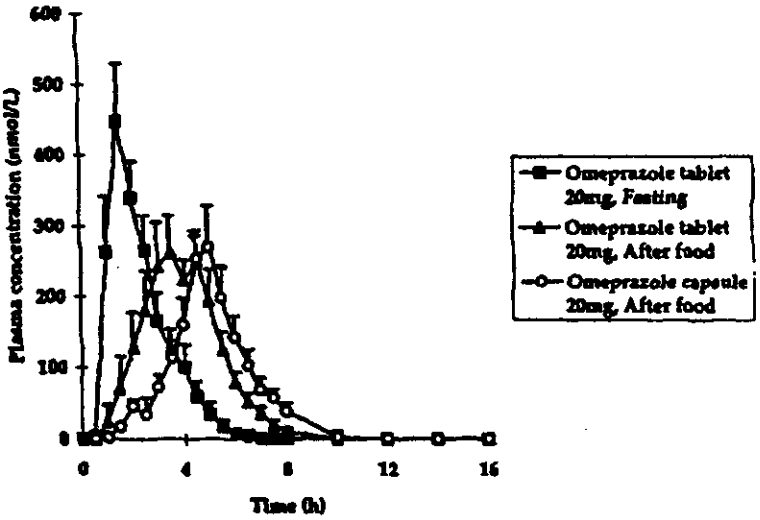


Fig. 10. Mean plasma levels after administration of single dose 20 mg omeprazole as a MUPS tablet (Fed and fasting states) or capsule (fed state).

Table 2. Least squares estimates for the treatment ratios of AUC and C_{max}

	AUC	C_{max}
Tablet (Fed)/ Tablet (Fasting)	1.20 (1.01-1.42)*	0.66 (0.51-0.86)

* 95% Confidence Interval

4.2. Relevant Drug-Drug Interactions

Both clarithromycin and diazepam interact to a significant extent with omeprazole 20 mg. Caution needs to be exercised when co-administering omeprazole with either clarithromycin or diazepam.

This section will only deal with interactions considered of potential clinical relevance. A complete listing of all drug-drug interaction studies related to omeprazole are included in a table format in Appendix 2.

a) Clarithromycin

In an open-label, randomized, four-way, cross-over study (Study SH-OMH-0014), healthy subjects received omeprazole, 20 mg bid, metronidazole, 400 mg bid, or clarithromycin, 250 mg bid, for 7 days or the triple combination twice daily for 7 days.

The results of the study suggested that pharmacokinetics of clarithromycin, metronidazole and their major metabolites were not significantly altered by

combination with omeprazole. However, the AUC and C_{max} for omeprazole were 100% and 60% higher, respectively, with combination therapy compared to omeprazole monotherapy (Table 3, Fig. 11).

Another study (Study SH-OMH-0016) that utilized an identical study design to that of study SH-OMH-0014 evaluated the interaction of omeprazole, 20 mg bid, with amoxycillin, 1 g bid, and clarithromycin, 500 mg bid The AUC and C_{max} for omeprazole were 110% and 68% higher, respectively, with combination therapy compared to omeprazole monotherapy (Table 4, Fig. 12). The results corroborate earlier findings in study SH-OMH-0014. The relevance of a 100% and 60% increase in AUC and C_{max} of omeprazole, respectively, is not clear. Thus, caution needs to be exercised when co-administering clarithromycin with omeprazole.

Table 3. Geometric mean estimates of the primary PK parameters for omeprazole in study SH-OMH-0014

	C_{max} (μM)	t_{max} (hr)	AUC (μM·hr)	$t_{1/2}$ (hr)
Omeprazole alone (O)	1.86 (1.43-2.42)*	1.50 (0.75-10.0)	3.67 (2.51-5.37)	1.05 (0.98-1.23)
Omeprazole triple therapy (OCM/O)	2.96 (2.28-3.86)	1.26 (0.75-3.00)	7.19 (4.91-10.52)	1.30 (1.11-1.52)
(OCM/O)	1.59 (1.25-2.04)	0.84 ND	1.96 (1.62-2.36)	1.24 (1.14-1.34)

* 95% Confidence interval

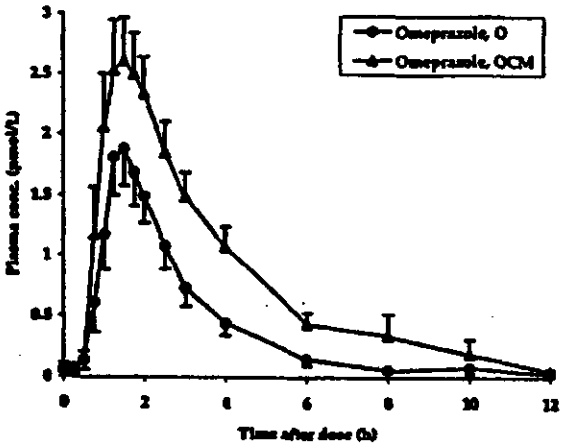


Fig. 11. Mean omeprazole plasma levels on day 7 both following administration of omeprazole, 20 mg bid, alone and in combination with metronidazole and clarithromycin.

Table 4. Geometric mean estimates of the primary PK parameters for omeprazole in study SH-OMH-0016

	C_{max} (μM)	t_{max} (hr)	AUC (μM·hr)	$t_{1/2}$ (hr)
Omeprazole alone (O)	1.45 (1.10-1.91)*	1.50 (0.75-2.50)	2.68 (1.82-3.94)	0.92 (0.75-1.13)
Omeprazole triple therapy (OCA/O)	1.68 (1.31-2.16)	1.09 ND	2.10 (1.85-2.38)	1.32 (1.13-1.53)

* 95% Confidence interval

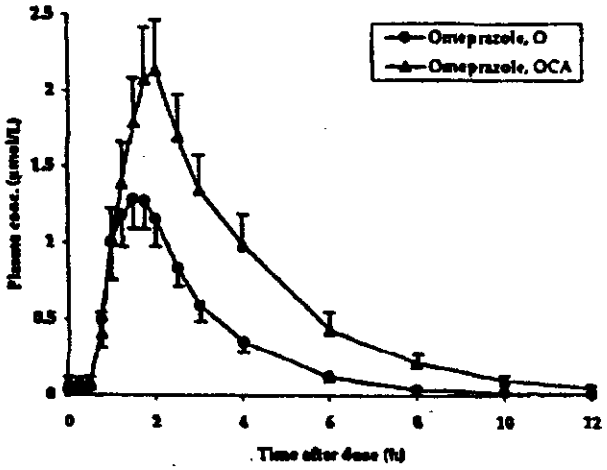


Fig. 12. Mean omeprazole plasma levels on day 7 both following administration of omeprazole, 20 mg bid, alone and in combination with amoxicillin and clarithromycin.

b) Diazepam

In an open-label, two-way cross-over study (Study I-285), healthy subjects received diazepam (0.1 mg/kg, I.V.) both alone and after 7 days of daily dosing of omeprazole, 40 mg. Diazepam and its desmethyl metabolite were assessed in plasma over a 72 hr period after diazepam administration in each treatment arm.

The results indicate that while CL decreased by 56% with concomitant omeprazole treatment, $AUC_{0-\infty}$ for diazepam increased by 142%. The results suggest that the elevated diazepam levels might be due to inhibition of CYP 450 metabolic enzymes. This notion is corroborated by the reduced formation of the desmethyl metabolite by 34% during omeprazole treatment. In another similar study [Gugler et al, 1985], CL of diazepam decreased by 54% with concomitant administration of omeprazole, 40mg.

A study by Andersson et al. in 1990 showed a 27% reduction in CL of diazepam when administered after 7 days of once daily omeprazole, 20 mg treatment, thus suggesting dose-dependent inhibition of diazepam metabolism by omeprazole. A study evaluating diazepam-omeprazole interaction in slow and rapid metabolizers (Study I-306-B) showed that omeprazole 20 mg increased diazepam AUC by 47% in slow metabolizers and 70% in rapid metabolizers.
The relevance of up to 70% increase in AUC of diazepam is not clear. However, in a study conducted to evaluate the clinical consequences of diazepam-cimetidine interaction, Greenblatt et al. reported that increases in diazepam and desmethyl-diazepam plasma levels by 62% and 54%, respectively, did not seem to translate into clinically relevant changes in effect. It should be noted, nevertheless, that the study included a small number of patients (n = 10), who were all under 50 years of age and who had been receiving a constant dose of diazepam for several months before the study. Caution needs to be exercised when co-administering diazepam with omeprazole.

4.3. Special populations

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 m^2, the disposition of omeprazole was very similar to that in healthy volunteers

In patients with chronic hepatic disease, the bioavailability increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours.

In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in some Asian subjects compared to Caucasians.

Dosage adjustment needs to be considered for the hepatically impaired and Asian subjects, particularly where maintenance of healing of erosive esophagitis is indicated.

The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers.

Omeprazole may interfere with absorption of drugs that depend on gastric pH for bioavailability such as ketoconazole, digoxin and iron salts.

5. Is the selected dissolution methodology for omeprazole MUPS tablets an appropriate surrogate for bioavailability and bioequivalence?

The selected dissolution method is an appropriate surrogate for bioavailability and bioequivalence of 20 mg omeprazole MUPS tablets in cases of changes in composition, manufacturing processes and manufacturing sites.

The proposed dissolution rate test for omeprazole MUPS tablets is as follows:

Pre-exposure ——— stage): Capsule is exposed for 2 hrs in USP apparatus II (paddle) to ——ml of ————————

Drug Release (- —— stage): In USP apparatus II (paddle) ——ml of ——— is added to the medium containing the capsule to give —— with a pH of 6.8. After ——— the release of H 199/18 is determined by UV detection at——nm. Sampling started immediately after addition of the buffer and was performed at least every minute for 12 individual tablets at each time point. The specifications mandate a Q = —— in 30 min for acceptance

A study was conducted (Study SH-OME-0025) to evaluate and establish an *in vitro/in vivo* correlation (IVIVC) for dissolution testing of omeprazole magnesium MUPS tablets. The following 4 formulations were utilized throughout the study:

- **Tablet A**: rapid release, To-Be-Marketed tablet formulation
- **Tablet B**: intermediate release tablet formulation
- **Tablet C**: slow release tablet formulation
- **Omeprazole suspension** 20 mg (reference formulation)

In vitro dissolution-time profiles were determined for tablets A, B and C using the earlier specified dissolution method (Fig. 13). *In vivo* dissolution-time profiles were obtained by deconvolution using results of an *in vivo* bioavailability study, which evaluated bioavailabilities of tablets A, B, C and the oral suspension (Fig. 14).

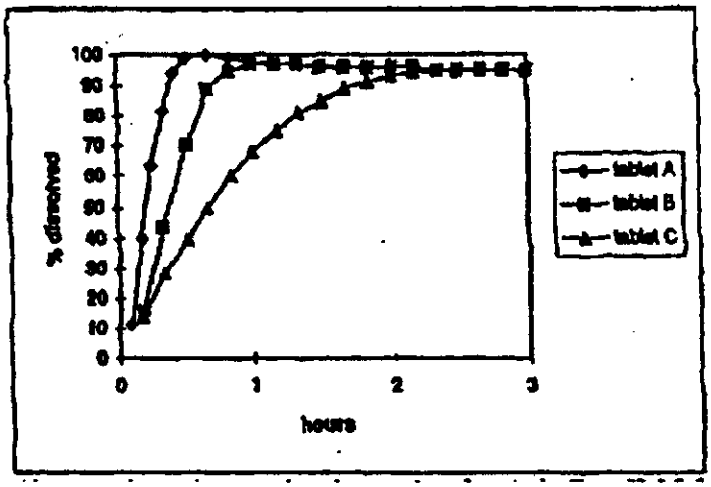


Fig. 13. Mean in vitro dissolution-time profile in pH 6.8 for tablets A, B and C

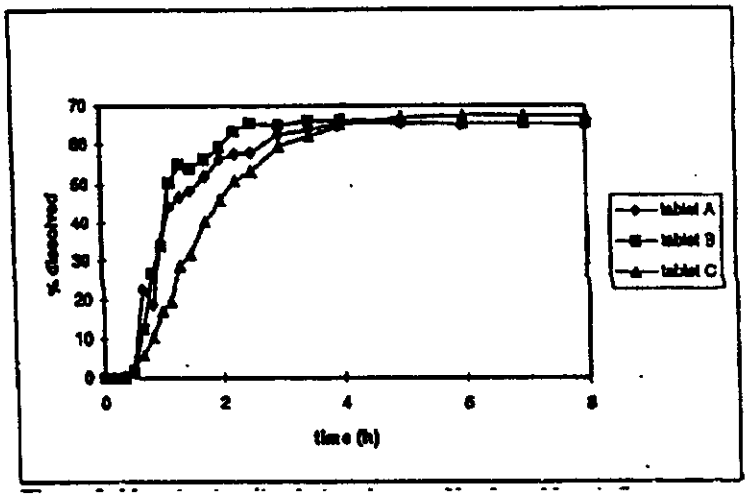


Fig. 14. Mean in vivo dissolution-time profiles for tablets A, B and C

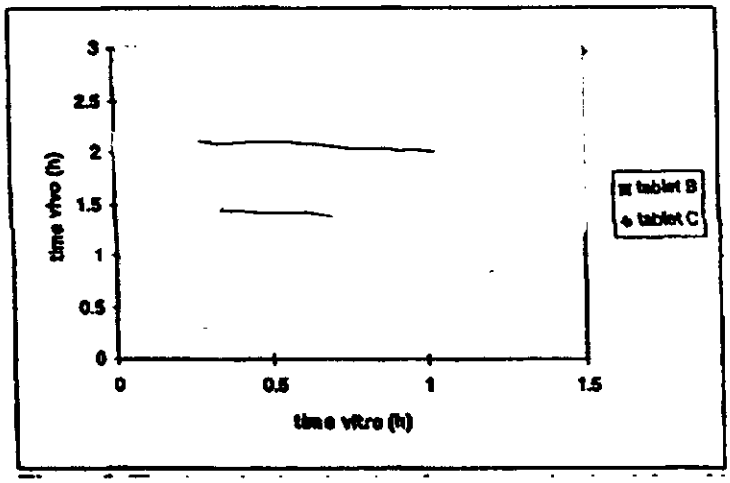


Fig. 15. The time in vitro vs. time in vivo for tablets B and C when equal fractions of drug have been dissolved in vitro and in vivo.

Due to the lack of difference between tablets A and B on their *in vivo* dissolution-time profiles, the IVIVC was based on tablets B (intermediate release) and C (slow release). This observed lack of difference *in vivo* between tablets A and B may be explained by the gastric emptying being the rate limiting step in the absorption process rather than *in vivo* dissolution. Thus, the apparent *in vivo* dissolution-time profile determined by deconvolution is likely to reflect gastric-emptying-time profile rather than *in vivo* dissolution-time profile.

A level A correlation was established by the *in vitro* dissolution method for formulations with an *in vitro* dissolution of —, or less at 30 min (Fig. 15). For tablets with faster dissolution rates than the upper limit of the IVIVC model, as tablet A (TBM formulation), faster dissolution is unlikely to result in significant differences in bioavailability.

The selected dissolution method was shown to be predictive and discriminative with respect to bioavailability characteristics for the studied tablets, and hence, it is deemed an acceptable surrogate test for bioavailability and bioequivalence in cases of changes in composition, manufacturing processes and manufacturing sites for omeprazole magnesium MUPS tablets with *in vitro* dissolution of ——or less at 30 min.

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Clinical Pharmacology (Phase I) Investigations

Study No./ [Reference]	Dose Form.	Design/Treatment	No. Subjects/ Age	Criteria for Evaluation	Summary of Results
I-1235 [Ref(s). 55]	Test: 20 mg MUPS capsules 20 mg MUPS tablet (six different pharmaceutical formulations) Reference: 20 mg commercially available capsule†	Study Part I & II identical: Open, randomized, single dose, 4-way cross over designs, 6 days w/o between investigational days.	In total 17 Healthy males 20-38 years Part I: 9 (8 evaluable) Part II: 8	Comparison of omeprazole PK after doses of Ome-Mg pellets with different release patterns & manufacturing techniques than the commercial capsule	Part I: 3 suspension layered MUPS formulations comparable bioavailability (AUC, C_{max}, t_{max}) to the commercial capsule. Part II: 3 extruded/ spheronized MUPS formulations comparable AUC to the commercial capsule but C_{max} ↓ ( ) and t_{max} delayed (p = 0.0240).
SH-OME-0001 [Ref(s). 57]	Test: 20 mg MUPS tablets (two different enteric coating compositions) Reference: 20 mg commercially available capsule†	Open, randomized, single dose, 3-way cross over study, 6 days w/o between investigational days.	8 healthy males; 23-35 years	Comparison of omeprazole PK after doses of MUPS tablets (Ome-Mg) to that of the commercial capsule	PK parameters comparable (AUC, C_{max} and t_{max}) between MUPS tablets and commercial capsule. However, one of the MUPS tablets gave statistically significantly higher AUC than the capsule (ratio = 1.14, 1.04-1.25; p = 0.0076).
SH-OME-0002 [Ref(s). 58]	Test: 20 mg MUPS tablet (intended commercial formulation) Reference: 20 mg commercially available capsule†	Open, randomized, 2-way cross over study, 6 days repeated o.d. dosing with 6 days w/o between periods.	29 (28 evaluable) healthy males; 20-30 years	Bioequivalence (criteria: 90% CI, 0.80-1.25 for AUC; C_{max}); evaluated after first (Day 1) and last dose (Day 6)	Bioequivalence established after 1st and last dose. $AUC_{Day\ 1}$ 1.02 (0.94-1.11); $AUC_{Day\ 6}$ 1.06 (0.95-1.17); $C_{maxDay\ 1}$, C_{maxDay} t_{max} was comparable after 1st and last dose.

* Study OME-0007 has not been reviewed since it employed the European-marketed formulation of omeprazole (Losec®). In addition, studies I-1235 and OME-0001 were not reviewed due to lack of direct relevance to the current submission.

Clinical Pharmacology (Phase 1) Investigations

Study No./ [Reference]	Dose Form.	Design/Treatment	No. Subjects/ Age	Criteria for Evaluation	Summary of Results
SH-OME-0007 [Ref(s). 59]	Test: 10 mg MUPS tablet 40 mg MUPS tablet (intended commercial formulation, 10 mg) Reference: 10 mg and 40 mg commercially available capsules†	Open, randomized, single dose, 4-way cross over study, 6 days w/o between investigational days.	32 healthy males; 20-36 years	Bioequivalence (criteria: 90% CI, 0.80-1.25 for AUC & C_{max}); evaluated after single doses.	Bioequivalence established for 10 & 40 mg tablets. 10 mg tabl.: AUC 1.01 (0.92-1.11); C_{max} ——— 40 mg tabl.: AUC 0.97 (0.88-1.06); C_{max} ——— t_{max} was similar for test and reference.
SH-OME-0008 [Ref(s). 60]	Test: 20 mg MUPS tablet (intended commercial formulation) Reference: 20 mg commercially available capsule†	Open, randomized, single dose, 3-way cross over study, MUPS tablet administered with and without food; Capsule given with food. 6 days w/o between investigational days.	18 healthy males; 20-38 years	Compare rate and extent of bioavailability between tablet and capsule after food intake. Assess effect of food on bioavailability of MUPS tablet.	The AUC ratio between tablet & capsule was 1.2 (95% CI: 1.01-1.42), with a C_{max} ratio of —— (95% CI: 0.95-1.60). Absorption was delayed (t_{max} fast 1.5 h, t_{max} fed 3.5 h), and C_{max} ↓. AUC ratio fed/fast 1.00 (95% CI: 0.84-1.18) for the MUPS tablet.
SH-OME-0009 [Ref(s). 61]	Test: 20 mg MUPS tablet (intended commercial formulation) Reference: 20 mg commercially available capsule†	Open, randomized, 2-way cross over study, 6 days repeated o.d. dosing with 14 days w/o between periods.	43 (36 evaluable) symptomatic GERD patients (32 M/11 F); 20-40 years	PD: Effects on intragastric acidity by 24-h pH monitoring on Day 6 of each period. PK: evaluate PK at steady state after tablets and capsules.	PD: 24 h intragastric pH identical (% time with pH≥4: 35% for both MUPS tablet and capsule) PK: AUC slightly ↓ (16%) for tablet compared with capsule. C_{max} ↓ (29%) for tablet compared with capsule.

Clinical Pharmacology (Phase 1) Investigations

Study No./ [Reference]	Dose Form.	Design/Treatment/Phase	No. Subjects/ Age	Criteria for Evaluation	Summary of Results
[Ref(s). 56;63]	Test: 20 mg MUPS tablets (low, intermediate and high *in vitro* drug-release rates). Reference: 20 mg omeprazole suspension	Open, randomized, single dose, 4-way cross over study, 7 days w/o between investigational days.	16 healthy males; 22-44 years	Comparison of bioavailability (AUC, C_{max}) between three MUPS tablets with different *in vitro* drug release rates.	The AUC and C_{max} were lower for the MUPS tablets than for the suspension. For the slow and intermediate release versus the fast release MUPS tablets the ratios of AUC and C_{max} were close to one, except for C_{max} ratio for slow release versus fast release MUPS, which was —— The *in vitro* dissolution method provides a basis for evaluation of *in vivo* relevance of the *in vitro* dissolution test method.
[Ref(s). 62]	Test: 10 mg and 20 mg MUPS tablets (intended commercial formulation) Reference: 20 mg commercially available US capsule	Open, randomized, single dose, 3-way cross over study, > 5 days w/o between investigational days.	30 healthy males; 18-40 years	Comparison of bioavailability (AUC, C_{max}) between two MUPS tablets with different strengths and the commercial US capsule.	The bioavailability of the MUPS tablets similar to that of the US commercial capsule 20 mg

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Appendix 2

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Summary table of drug-drug interaction studies with omeprazole vs. diazepam, phenytoin, warafarin 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	-	-	21, 22
Diazepam	Healthy subjects (n=12)	0.1/kg (iv)	20 x 7 days***	-27	-	-	23, 24
Diazepam	Healthy subjects (n=10)	0.1/kg (iv)	20 x 7 days***	-26****	-	-	16, 25
Phenytoin	Healthy subjects (n=8)	250 (iv)	40 x 7 days***	-15	-	-	22, 26
Pheaytoin	Healthy subjects (n=10)	300	40 x 7 days***	-	+19	-	27, 28
Phenytoin	Healthy subjects (n=18)	4.5/kg	40 x 3 days***	-	NC	-	29
Phenytoin	Epileptic patients (n=8)	ss	20 x 21 days	-	-	NC	30, 31
Warfarin - *R* Warfarin - *S*	Healthy subjects (n=21)	4.7*	20 x 14 days	-	-	+12 NC	32.. 33
Warfarin - *R* Warfarin - *S*	Anticoag. Patients (n=28)	ss	20 x 21 days	-	-	+9.5 NC	34, 35
Clarithromycin	Healthy subjects (n=20)	500 tid**	40 x 6 days	-	+15	-	18
Clarithromycin	Healthy subjects (n=16)	250 bid**	20 bid x 7 days	-	NC	-	19
Clarithromycin	Healthy subjects (n=16)	500 bid**	20 bid x 7 days	-	NC	-	20

APPENDIX 1
Summary Table of Miscellaneous Drug-Drug Interaction Studies With Omeprazole Versus Other Drugs Not Described Elsewhere

Drug	Study population	Study Design	Drug dose (mg)	Omeprazole dose (mg)	Summary results	Reference
Effect of omeprazole on the pharmacokinetics of other drugs						
Acenocoumarol	Anticoagulated patients (n 118)	Parallel groups (the control group with 299 patients had no interfering treatment)	Long term - undefined doses	Undefined doses	No differences between the groups with regard to dose changes during treatment.	[1.]
Acenocoumarol	Healthy subjects (n 8)	Double-blind, placebo-controlled randomized, crossover	10 sd	40 x 2 days (3 days in total)	No effect on AUC, Cmax, tmax, or t1/2 of acenocoumarol or on any pharmacodynamic parameter (anticoagulation time).	[2.]
Amoxicillin	Healthy subjects (n=24)	Double-blind, double-dummy, crossover	750 bid x 5 days	40 bid x 5 days	No effect on the pharmacokinetics (AUC) of amoxicillin.	[3.]
Amoxicillin	Healthy subjects (n=8)	Double-blind, placebo-controlled randomized, crossover	750 sd, i.v.	40 bid x 5 days	No effect on CL, AUC, or Cmax of amoxicillin.	[4.]
Acetyl salicylic acid	Healthy subjects (n 8)	Randomized, crossover	500 sd	20 x 4 days	No effect on AUC, Cmax or t1/2 of acetyl salicylic acid.	[5.]
Bismuth	Healthy subjects (n=6)	Placebo controlled, crossover	240 sd (tripotassium dicitrat)	40 x 7 days	Increased (4 fold) absorption of bismuth due to the elevated pH caused by omeprazole.	[6.]

Doses are taken orally unless stated otherwise; sd = single dose; bid = twice daily; tid = three times daily; i.v. = intravenously
AUC = area under the plasma concentration versus time curve; Cmax = maximum plasma concentration; tmax = time to reach Cmax; t1/2 = plasma elimination half life; CL = clearance; EM = extensive metabolizer; PM = poor metabolizer.

APPENDIX 1 (Cont.)
Summary Table of Miscellaneous Drug-Drug Interaction Studies With Omeprazole Versus Other Drugs Not Described Elsewhere

Drug	Study population	Study Design	Drug dose (ng)	Omeprazole dose (mg)	Summary results	Reference
Bupivacaine	Patients (n=10+10)	Parallel groups	80 sd	40 x 1 day	No effect on AUC, Cmax, tmax, (or t1/2) of bupivacaine.	[7.]
Cerivastatin	Healthy subjects (n=12)	Open label, randomized, crossover	0.3 sd	20 x 5 days	No effect on AUC, Cmax, tmax, or t1/2 of cerivastatin.	[8.]
Chloroguanide	Healthy subjects (n=20)	Open label, randomized, crossover	200 sd	40 x 7 days	The chloroguanide to cycloguanil metabolic ratio, which inversely reflects CYP2C19 activity, increased by more than 2 fold. This is a result of CYP2C19 inhibition by omeprazole.	[9.]
Clarithromycin	Healthy subjects (n=8)	Double-blind, placebo-controlled randomized, crossover	500 ad, iv.	40 bid x 5 days	No effect on CL, AUC or Cmax of clarithromycin.	[4.]
Diazepam	Healthy subjects (Japanese, n=15; 9 EM & 6 PM)	Single-blind, randomized, crossover	0.1/kg, sd, i.v.	20 x 8 days (23 days in total)	Both AUC and t1/2 of diazepam increased by 25% and the CL decreased by 21% in EM. No effect in PM. This is a result of CYP2C19 inhibition by omeprazole.	[10.]
Diazepam	Healthy subjects (n=15; 8 Caucasian & 7 Chinese)	Double-blind, randomized, crossover	10 sd	40 x 8 days (21 days in total)	Oral CL of diazepam decreased by 38% in Caucasians and by 21% in Chinese. T1/2 was prolonged by 42% in Caucasians but was unchanged in Chinese. This is a result of CYP2C19 inhibition by omeprazole.	[11.]

Doses are taken orally unless stated otherwise; sd = single dose; bid = twice daily; tid = three times daily; i.v. = intravenously
AUC = area under the plasma concentration versus time curve; Cmax = maximum plasma concentration; tmax = time to reach Cmax; t1/2 = plasma elimination half life; CL = clearance; EM = extensive metabolizer; PM = poor metabolizer.

APPENDIX 1 (Cont.)
Summary Table of Miscellaneous Drug-Drug Interaction Studies With Omeprazole Versus Other Drugs Not Described Elsewhere

Drug	Study population	Study Design	Drug dose (mg)	Omeprazole dose (mg)	Summary results	Reference
Digoxin	Elderly patients (n=22)	Baseline + concomitant treatment ("crossover")	0.125-0.25 daily, chronic treatment	20 x 10 days	No effect on serum digoxin levels.	[12.]
Doxycycline	Healthy subjects (n=24)	Open label, randomized, crossover	100 sd, monohydrate vs carrageenate	40 x 7 days	No effect on AUC, Cmax, tmax, or t1/2 of the carrageenate but 38% decreased AUC and 45% decreased Cmax of the monohydrate due to the elevated pH caused by omeprazole.	[13.]
Ethanol	Healthy subjects (n=7)	One sequence ("crossover")	0.3 g/kg, sd	20 x 7 days	No effect on AUC or Cmax of ethanol.	[14.]
Ethanol	Healthy subjects (n=8)	One sequence ("croesover")	0.5 g/kg, sd	20 bid x 6 days	No effect on AUC, Cmax, tmax, or Ke (elimination constant) of ethanol.	[15.]
Ethanol	Healthy subjects (n=19)	("Crossover")	0.6 g/kg, sd, i.v. and oral	20 x 14 days	No effect on AUC or Cmax of ethanol.	[16.]
Fluconazole	Healthy subjects (n=12)	Randomized, crossover	100 sd	20 x 7 days	No effect on AUC, Cmax, tmax, or t1/2 of fluconazole.	[17.]

Doses are taken orally unless stated otherwise; sd = single dose; bid = twice daily; tid = three times daily; i.v. = intravenou sly
AUC = area under the plasma concentration versus time curve; Cmax = maximum plasma concentration; tmax = time to reach Cmax; t1 /2 = plasma elimination half life; CL = clearance; EM = extensive metabolizer; PM = poor metabolizer.

APPENDIX 1 (Cont.)
Summary Table of Miscellaneous Drug-Drug Interaction Studies With Omeprazole Versus Other Drugs Not Described Elsewhere

Drug	Study population	Study Design	Drug dose (mg)	Omeprazole dose (mg)	Summary results	Reference
Ketoprofen	Healthy subjects (n=12)	Double-blind, randomized, crossover	100 sd	20 x 1 day	No effect on AUC, Cmax, tmax, or t1/2 of ketoprofen.	[18.]
Mesalazine	Healthy subjects (n=20)	One sequence ("crossover")	400 tid x 21 days	20 x 7 days, 20 bid x 7 days	No effect on urinary and fecal excretion of 5-ASA and N-acetyl 5-ASA.	[19.]
Metronidazole	Healthy subjects (n=8)	Double-blind, placebo-controlled randomized, crossover	400 sd, i.v.	40 bid x 5 days	No effect on CL, AUC or Cmax of metronidazole.	[4.]
Metronidazole	Healthy subjects (n=8)	Double-blind, placebo-controlled, randomized, crossover	400 sd, i.v. and oral	40 bid x 5 days	No effect on the pharmacokinetics of neither the i.v.(CL, AUC, t1/2) nor the oral (AUC, Cmax, tmax, t1/2) dose of metronidazole.	[20.]
Metronidazole	Healthy subjects (n=8)	Open label, randomized, crossover	400 sd	20 bid x 5 days	No effect on AUC, Cmax, tmax, or t1/2 of metronidazole.	[21.]
Mexiletine	Healthy subjects (Japanese, n=9)	One sequence ("crossover")	200 sd	40 x 7 days	No effect on AUC, Cmax, Ka (absorption constant), or t1/2 of mexiletine.	[22.]

Doses are taken orally unless stated otherwise; sd = single dose; bid = twice daily; tid = three times daily; i.v. = intravenously
AUC = area under the plasma concentration versus time curve; Cmax = maximum plasma concentration; tmax = time to reach Cmax; t1 /2 = plasma elimination half life; CL = clearance; EM = extensive metabolizer; PM = poor metabolizer.

APPENDIX 1 (Cont.)
Summary Table of Miscellaneous Drug-Drug Interaction Studies With Omeprazole Versus Other Drugs Not Described Elsewhere

Drug	Study population	Study Design	Drug dose (mg)	Omeprazole dose (mg)	Summary results	Reference
Nicotinamide	Healthy subjects (n=5)	"Crossover"	3 g, sd	20 x 2 days	No effect on Cmax or tmax of nicotinamide.	[23.]
Proguanil	Healthy subjects (n=12)	Randomized, crossover	100 sd	20 x 1 day	No effect on the urinary excretion of proguanil or cycloguanil and no effect on the metabolic ratio.	[24.]
Proguanil	Healthy subjects (n=12)	Crossover	200 sd	40 x 7 days	Apparent oral clearance of proguanil decreased by 32%. This is a result of CYP2C19 inhibition by omeprazole.	[25.]
Quinolone antibiotics;	Healthy subjects					
Ciprofloxacin	(n=12)	Double-blind, randomized, crossover	500 sd	20 x 4 days	No effect on AUC, Cmax, tmax, or t1/2 of ciprofloxacin	[26.]
Lomefloxacin	(n=12)		400 sd	20 x 4 days	No effect on AUC, Cmax, tmax, or t1/2 of lomefloxacin	[26.]
Trovafloxacin	(n=12)	Randomized, crossover	300 sd	40 x 2 days (2 hours prior to dosing)	AUC and Cmax of trovafloxacin decreased by 18 and 32%, respectively, while t1/2 was unchanged. This is probably due to the elevated pH caused by omeprazole.	[27.]

Doses are taken orally unless stated otherwise; sd = single dose; bid = twice daily; tid = three times daily; i.v. = intravenously
AUC = area under the plasma concentration versus time curve; Cmax = maximum plasma concentration; tmax = time to reach Cmax; t1 /2 = plasma elimination half life; CL = clearance; EM = extensive metabolizer; PM = poor metabolizer.

APPENDIX 1 (Cont.)
Summary Table of Miscellaneous Drug-Drug Interaction Studies With Omeprazole Versus Other Drugs Not Described Elsewhere

Drug	Study population	Study Design	Drug dose (mg)	Omeprazole dose (mg)	Summary results	Reference
Effect of other drugs on the pharmacokinetics of omeprazole						
Amoxicillin	Healthy subjects (n=24)	Double-blind, double-dummy, crossover	750 bid x 5 days	40 bid x 5 days	No effect on the pharmacokinetics (AUC) of omeprazole.	[3.]
Antacids	Healthy subjects (n=6)	Randomized, crossover	170 mmol buffering capacity	30 sd	No effect on AUC, Cmax or tmax, of omeprazole.	[28.]
Carbamazepine	Patients (n=5)	One sequence ("crossover")	400-600 x 21 days	20 sd	AUC of omeprazole decreased by 40% consequent to CYP3A4 induction by carbamazepine.	[29.]
Ketoconazole	Healthy subjects (n=10; 5 EM & 5 PM)	Crossover	50, 100 or 200 x 4 days	20 sd	AUC and Cmax of omeprazole increased by 36 and 40%, respectively, in EM and by 99 and 46% in PM consequent to CYP3A4 inhibition by 100 and 200 mg of ketoconazole. T1/2 was unchanged in EM but increased by approximately 50% in PM. 50 mg of ketoconazole only showed partial inhibition.	[30.]
Metoclopramide	Healthy subjects (n=6)	Randomized, crossover	10 sd	30 sd	No effect on AUC, Cmax or tmax, of omeprazole.	[28.]

Doses are taken orally unless stated otherwise; sd = single dose; bid = twice daily; tid = three times daily; i.v. = intravenously
AUC = area under the plasma concentration versus time curve; Cmax = maximum plasma concentration; tmax = time to reach Cmax; t1 /2 = plasma elimination half life; CL = clearance; EM = extensive metabolizer; PM = poor metabolizer.

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Appendix 3

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List of Analytical Methods Utilized in Clinical Pharmacology and Biopharmaceutics studies

Pharmacokinetic Studies

Protocol	Method	Method Number
I-1235	Liquid Chromatography	
SH-OME-0025	Liquid Chromatography and	
SH-OME-0001	Liquid Chromatography	
SH-OME-0002	Liquid Chromatography	
SH-OME-0007	Liquid Chromatography	
SH-OME-0008	Liquid Chromatography	
SH-OME-0009	Liquid Chromatography	
AMI 200	Omeprazole LC/MS/MS	Archival NDA 21-229 folder .pdf, pdf pages 263-299

[a] Method . was filed to NDA 21-229 on 4/28/00 in response to FDA 4/14 Information Request letter.

Drug Interaction Studies

Protocol	Method	Method Number
I-212	Liquid Chromatography	
SH-OMH-0014	Liquid Chromatography	
SH-OMH-0016	Liquid Chromatography	
I-285	Liquid Chromatography and	
I-306	Liquid Chromatography	
I-306b	Liquid Chromatography	
I-286	Liquid Chromatography and	
I-289	Liquid Chromatography - only	
I-362	Liquid Chromatography - only	
I-293	Liquid Chromatography	
I-367	Liquid Chromatography – samples only.	

Other Studies

Protocol	Method	Method Number
129	, only	N/A
131	nly	N/A
RPEX 23502	In vitro / in vivo correlation report	Refer to SH-OME-0025 for in vivo data Method

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Appendix 4

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3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling