

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-153/ 21-154

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review**NDA:** 21-153**Code:** 2S**Trade Name:** Nexium™ Delayed-Release Capsules**Stamp Date:** 12/3/1999**Active Ingredient:** Esomeprazole Sodium**Related INDs:** _____
_____**Sponsor:** AstraZeneca Pharmaceuticals**Statistics Consultant:** Donald J. Schuirmann**Reviewer:** Suliman I. Al-Fayoumi, Ph.D.**Type of Submission:** Original NDA (NME)**Synopsis**

Esomeprazole (H 199/18), the S-enantiomer of omeprazole, is a potent inhibitor of gastric Acid secretion. It has been proposed for the treatment of a variety of acid-related diseases such as gastroesophageal reflux disease (GERD) and erosive esophagitis (EE).

The sponsor has adequately characterized the clinical pharmacology and biopharmaceutics-related aspects of the drug. H 199/18 is well absorbed with an absolute bioavailability of 90% after repeated-dose administration. The extent of exposure (AUC) for H 199/18 correlates well with inhibition of gastric acid secretion, indicating that response is dose-related.

H 199/18 is highly bound to plasma proteins (97%). It is extensively metabolized by hepatic CYP-450 isozymes, primarily CYP 2C19 and CYP 3A4, to hydroxy and sulphone metabolites. Up to 80% of the oral dose is excreted as inactive metabolites in the urine. Additionally, less than 1% of the oral dose is excreted in urine as unchanged drug. Dosage adjustment is warranted for H 199/18 in moderate and severe hepatic dysfunction, but not in renal failure. Total clearance of H 199/18 is reduced from 17 L/hr after a single dose to 9 L/hr after repeated-dose administration indicating that H 199/18 exhibits time-dependent pharmacokinetics. The AUC for H 199/18 is reduced by 44% after food intake indicating a significant food effect.


C_{max} and AUC of H 199/18 were elevated in elderly and female subjects relative to young male subjects. The clinical trial- and to-be-marketed formulations were shown to be bioequivalent.

Significant metabolic drug-drug interactions were shown for H 199/18 with diazepam and clarithromycin.

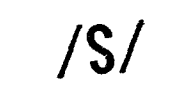
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Recommendations:

The Human Pharmacokinetics and Bioavailability section of NDA 21-153 submitted on 12/6/1999 is acceptable from the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics. Clinical Pharmacology and Biopharmaceutics-related changes to the sponsor's proposed labeling needs to be conveyed to the sponsor as deemed appropriate.

 /S/ 9/18/00

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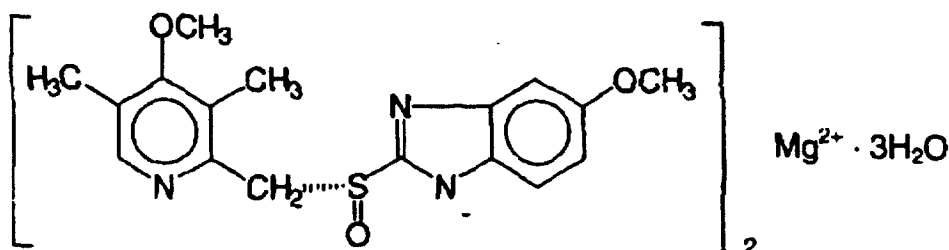
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SUMMARY

1. What is the pharmacological class, scientific rationale and intended use of H 199/18 (esomeprazole)?



H 199/18 is the S-enantiomer of omeprazole, a potent inhibitor of gastric acid secretion and the first proton pump inhibitor approved in the US in 1989. *In vitro* studies as well as animal studies have demonstrated equipotent activity of omeprazole and its two enantiomers on gastric acid secretion. As omeprazole treatment has not been successful in all patients with acid-related diseases, H 199/18 was developed by AstraZeneca Pharmaceutical Company with the intention of further optimizing the treatment of acid-related diseases. At present, H 199/18 is not approved in any country,

The sponsor's proposed indications include; healing and maintenance of Erosive Esophagitis, treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD)

The proposed dosage is either 20 or 40 mg once daily for 4-8 weeks.

2. What are the physicochemical properties of H 199/18 and the composition of the to-be-marketed (TBM) capsule formulation?

Esomeprazole is highly unstable in acidic media, therefore it has been formulated as enteric-coated pellets.

The partition coefficient for H 199/18 between n-octanol and water was determined as $\log K_D = 2.24$. The stable form in water for H 199/18 magnesium is a trihydrate. The solubility of H 199/18 magnesium trihydrate in water is 1.5 mg/ml with a corresponding pH of 10.0.

Esomeprazole magnesium has been formulated as delayed-release capsules for oral administration. Each capsule contains 20 mg or 40 mg esomeprazole formulated in enteric-coated pellets. The two strengths are compositionally proportional. The composition of the formulation for each strength is shown in table 1.

Table 1. Composition of the TBM Nexium capsule

Ingredients	20 mg Capsule (mg)	40 mg Capsule (mg)	Function
H 199/18 (as H 199/18 magnesium trihydrate)	20 (22.3)	40 (44.5)	Active ingredient
Glyceryl monostearate 40-50	—	—	—
Hydroxypropyl Cellulose	—	—	—
Hydroxypropyl Methylcellulose	—	—	—
Magnesium Stearate	—	—	—
Methacrylic Acid Copolymer Type C	—	—	—
Polysorbate 80	—	—	—
Sugar spheres	—	—	—
Talc	—	—	—
Triethyl Citrate	—	—	—
Hard gelatin capsules	—	—	—

3. Is there a pharmacokinetic/pharmacodynamic relationship for H 199/18?

The % inhibition of pentagastrin-stimulated acid secretion showed good correlation with AUC (exposure) of H 199/18, with a lower AUC needed for maximal inhibition of acid secretion on day 5 relative to day 1.

A dose-response study of H 199/18 sodium on pentagastrin-stimulated gastric acid secretion in healthy subjects at doses of 5, 10 and 20 mg showed that the antisecretory effect of H 199/18 is dose dependent, with an increased effect upon repeated daily dosing which is likely related to the cumulative effect of H 199/18 on the inhibition of gastric acid secretion (Study QBE-0002).

A second study compared 20 mg omeprazole to 20 and 40 mg H 199/18 on the effect on 24-hour intragastric pH and %time with pH > 4. The study failed to demonstrate a clear advantage of H 199/18 over omeprazole at a dose of 20 mg. In addition, the 40 mg dose of H 199/18 proved to be more effective than the 20 mg dose in elevating 24-hour intragastric pH as well as increasing %time with pH > 4 (Study QBE-0008). It is unclear, however, whether the observed differences in the pharmacodynamic markers would translate into clinically relevant differences in patients.

4. Were there any dose-related adverse events?

No dose-related serious adverse events were observed during the course of the clinical studies.

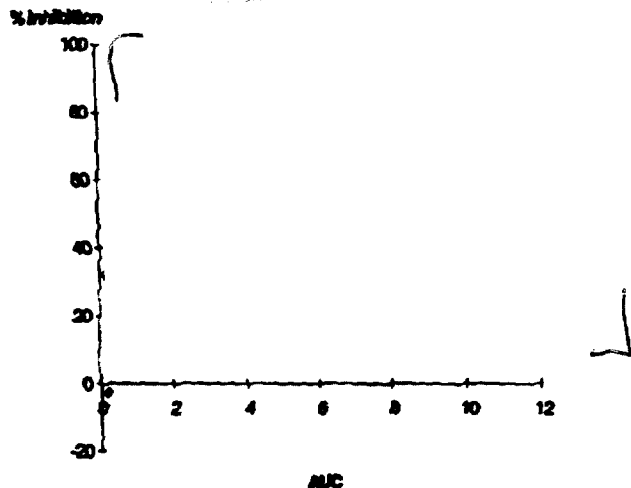


Figure 5. Inhibition (%) of pentagastrin stimulated acid output vs. AUC following administration of 5, 10 and 20 mg H 199/18 and 20 mg omeprazole respectively on day 5.

5. What does the mass balance studies contribute to understanding the disposition pathways of H 199/18 in man, and how does disposition of H 199/18 compare to that of omeprazole?

H 199/18 is well absorbed as evidenced by nearly complete excretion of oral doses of H 199/18 in urine and feces within 48 hrs of administration, with close to 80% of the dose excreted in urine. The metabolism of H 199/18 was extensive with less than 1% of the parent compound and more than 20 radiolabelled compounds separated from urine.

H 199/18 showed a very similar metabolic pattern to omeprazole in humans with extensive hepatic metabolism taking place. Nine major metabolites were identified in urine that were formed via hydroxylation of the 5-methylpyridine group and further oxidation to the corresponding carboxylic acid, and demethylation or hydroxylation of the benzimidazole moiety, followed by conjugation with glucuronic acid. The metabolites of H 199/18 are devoid of antisecretory activity.

H 199/18 and omeprazole differed in the effect of polymorphism on metabolism. Whereas AUC_{EM}/AUC_{PM} ratio was 2.9 for H 199/18, it was 5.3 for omeprazole (Study QBE-0024).

6. Based on in vitro metabolism studies, what is the known metabolic route of H 199/18 in man?

In vitro studies have identified CYP 2C19 and CYP 3A4 isoymes as the primary metabolic enzymes responsible for the formation of the major esomeprazole metabolites, the hydroxy and sulphone metabolites, respectively.

The data suggests that CYP 2C19 is the major metabolic enzyme for both R- and S-omeprazole. CYP 3A4 plays a bigger role in the metabolism of S-omeprazole compared to R-omeprazole, which might explain the lower AUC_{EM}/AUC_{PM} for S-omeprazole relative to the R enantiomer (Study #24113).



Fig. 1. Proposed metabolic pathway for H 199/18

What is the extent of plasma protein binding for H 199/18?

The protein binding of H 199/18 in human plasma is high (97%) and appears to be independent of gender and concentration within the studied range (2-20 $\mu\text{mol/L}$), which covers the relevant therapeutic blood levels. The sponsor did not attempt to characterize the binding protein, or the impact of disease state or drug-drug interactions on protein binding of H 199/18 (Study #24049).

7. How likely is S-omeprazole to invert to the R-enantiomer?

Two in vivo studies conducted in both PM and EM subjects showed that H 199/18 was optically-stable and the degree of inversion seemed to be negligible (Studies QBE-0001 & 0027)

8. What are the relevant bioavailability and ADME parameters for H 199/18?

A significant reduction (~30%) is apparent in total body clearance after both IV and oral multiple dose administration of H 199/18 relative to single dose administration, suggesting time dependent changes in pharmacokinetics.

The primary pharmacokinetic (PK) parameters after single and multiple dose administration of H 199/18 are summarized in table 2 (Studies QBE-0006 & 0045). The increased bioavailability observed with multiple administrations of 40 mg H 199/18 were not observed with the 20 mg dose, which points to saturable first-pass metabolism. Earlier published literature reports indicate that gastric acidity status has negligible effect on AUC of omeprazole enteric-coated granules. Thus, bioavailability of enteric-coated H 199/18 would not be expected to change irrespective of the gastric acidity status.

Table 2. Major PK parameters for H 199/18 after single and multiple 40 mg QD dose administration

	F (%)	AUC (Oral, $\mu\text{mol}\cdot\text{hr}/\text{L}$)	C_{max} (Oral, $\mu\text{mol}/\text{L}$)	CL (L/hr)	$t_{1/2}$ (hr)	V_{ss} (IV, L/kg)
Day 1	63.6	4.32	2.38	17.1	0.85	0.25
Day 5	88.9	11.21	4.64	9.2	1.25	0.22

9. Is the pharmacokinetics of H 199/18 linear?

H 199/18 exhibits non-linearity in pharmacokinetics within the dose range studied in the pivotal clinical trials.

H 199/18 exhibited dose proportionality with respect to C_{max} and AUC within the studied dose range of 5-20 mg after single dose (Study QBE-0002). However, a greater than proportional deviation from dose proportionality is observed for the 40 mg dose after a single dose. This is consistent with a known trend for omeprazole to exhibit a greater than linear response in peak plasma concentration and AUC with doses greater than 40 mg. After multiple dosing, a large deviation from dose proportionality is clear even at the lowest studied dose, which is likely due to time-dependent changes in PK.

10. Is the pharmacokinetics of H 199/18 different in patients?

The pharmacokinetics of H 199/18 in GERD patients is similar to that of young healthy subjects.

Since reduced intragastric pH in GERD patients is not anticipated to alter bioavailability of H 199/18, as expected, the PK of H 199/18 in GERD patients was similar to that in healthy subjects (Study QBE-0008).

11. How similar were the to-be-marketed and the clinical trial formulations of H 199/18?

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The TBM and clinical trial formulations were shown to be bioequivalent, and hence, interchangeable, under both fasting and fed conditions.

Throughout the bioequivalence (BE) studies, the sponsor utilized a two-stage, sequential, crossover BE design instead of the standard one stage, crossover BE design. In the sponsor's proposed two-stage BE design, an initial group of 36 subjects received the formulations in a standard two-treatment crossover design. If 94% CIs for the geometric mean ratios for T/R fell within the 80%-125% limits for all three PK parameters (AUC_{0-t} , $AUC_{0-\infty}$, C_{max}), the study would be terminated and a conclusion of BE would be reached. If this criteria was not met, an additional 36 subjects would be included, then 94% CI would again be calculated using data from both groups (n = 72). If the 94% CI intervals fell within the 80%-125% limits, BE would be concluded¹.

Four 20 mg and three 40 mg capsule formulations were used in the clinical studies. Two of the 20 mg formulations had identical composition but different shell sizes, and both were used in Phase I/II clinical studies. The two other formulations of the 20 mg capsules were also of identical composition but had different shell sizes, and were used in Phase III clinical studies as well as NDA stability studies. No direct bioavailability link was used between Phase I/II and Phase III formulations for the 20 mg dose. However, a cross-study comparison indicated that both were similar on their bioavailabilities.

Table 3. Summary of the primary PK parameters for Phase I/II and Phase II formulations for the 20 mg dose of H 199/18

	C_{max}	AUC_{0-t}
Phase I/II formulation (Study QBE-0008)	2.42	4.18
Phase III formulation (Study QBE-0033)	2.41	4.73

As for the 40 mg formulations, one formulation was used in Phase I/II clinical studies, while the other two were of identical composition but different shell sizes and were used in Phase III clinical studies as well as NDA stability studies. A study was conducted to compare Phase I/II and Phase III formulations on their relative bioavailabilities (Study QBE-0029). The relative bioavailability of the Phase III capsule relative to the Phase I/II capsule is 93%. The two capsule formulations were bioequivalent.

Included in the submission were several studies that were conducted to compare the bioavailabilities of _____ tablet formulation to the Phase II capsule under both fasting and fed states. The studies showed bioequivalence of the two formulations under both fasting and fed states.

¹ For further details and justification, see attached Biostatistics consult.

12. Is there a food effect on bioavailability and is it expected to influence dosing recommendations?

Food intake resulted in a delayed and reduced absorption of H 199/18 in both male and female subjects. Food seems to reduce oral bioavailability of H 199/18.

Three studies were conducted to evaluate the effect of food on PK/PD of H 199/18 in male and female subjects. All the studies showed a clear food-effect with AUC and C_{max} decreasing markedly with food intake. Altogether, C_{max} decreased by 56-79% and AUC by 33-53% after administration of a single 40 mg H 199/18 dose under fed conditions. Those PK differences between fasting and fed state were similar after multiple dosing, where C_{max} decreased by 53-68% and AUC by 26-50%.

Two of the studies showed a clearly greater food-effect in females compared to males. In one study, AUC and C_{max} decreased with food intake by 58% and 80% in females, respectively, while AUC and C_{max} in males only decreased by 24% and 51%, respectively (Study QBE-0025). Similar findings were observed in the other study (Study QBE-0030). Based on %time with pH > 4 (PD marker), it was reported in study QBE-0044 that the observed PK differences between fasting and fed state as well as between male and female subjects did not translate into significant PD differences. However, differences between males and females on their AUC on days 1 and 5 under fasting and fed state seemed to correlate well with differences in the %time with pH > 4. Thus, it seems likely that differences in PK may translate into measurable differences in PD.

The sponsor also conducted a study to compare the bioavailability of an intact 40 mg capsule to that of an open capsule that was mixed with applesauce. The two formulations were bioequivalent (Study #227). An open capsule mixed with applesauce may serve as an alternative mode of administration

It is stated under DOSAGE AND ADMINISTRATION section in the proposed Nexium labeling that "Nexium Delayed-Release Capsules should be swallowed whole and

Table 4. Summary of PK parameters for H 199/18 after administration of a single dose under fasting and fed conditions.

	Fasting State	Fed State
Study QBE-0025		
C_{max}	3.70	3.17
AUC	6.96	3.92
Study QBE-0030		
C_{max}	2.44	1.07
AUC	4.07	2.73
Study QBE-0044		
C_{max}	2.81	0.59
AUC	4.01	1.87

13. Is there a need for dosage adjustment in special populations (gender, pediatrics and geriatrics) and in disease states (renal and

hepatic impairment)?

13.1. Hepatic Impairment

Plasma levels of H 199/18 in patients with mild hepatic impairment were generally higher but within the same range as that noted for GERD patients. However, patients with moderate and severe hepatic impairment showed markedly higher plasma levels of H 199/18 when compared to those of GERD patients, which suggests that dosage adjustment of H 199/18 may be warranted in patients with moderate and severe hepatic impairment.

Consistent with a major role for hepatic metabolism in the elimination of H 199/18, it would be expected that hepatic impairment would affect the bioavailability and disposition of H 199/18. A study investigating the PK of H 199/18 in patients with mild, moderate and severe hepatic impairment indicated that a significant elevation in plasma levels of H 199/18 would be expected in moderate and severe hepatic impairment, where AUC_{0-1} increased by 76% and 134% and C_{max} by 14% and 38%, respectively. Hence, dosage adjustment is warranted in this group of patients (Study QBE-0026).

14.2. Renal Impairment

No dosage adjustment is warranted in subjects with any degree of renal impairment.

It would be expected that renal impairment would have little (if any) impact on H 199/18 PK. No studies have been conducted to evaluate the effect of renal impairment on H 199/18 PK, since less than 1% of an oral dose of H 199/18 is excreted intact in urine.

14.3. Gender

A consistent gender difference was observed in PK of H 199/18, where females had higher AUC and C_{max} compared to males.

A gender analysis of the results of all PK studies showed that females had around 30% and 14% higher C_{max} and AUC values compared to males after single and multiple dose administration, respectively. Since those differences are unlikely to be clinically relevant, dose adjustment is not warranted in female patients.

14.4. Pediatrics

The safety and effectiveness of H 199/18 has not been established in pediatric patients below 18 years of age.

The target population in the current submission does not include pediatrics. No studies have been conducted by the sponsor to assess the safety and effectiveness of H 199/18 in this patient population.

14.5. Geriatrics

An age increase of 20 years was estimated to give 6% and 15% higher C_{max} and AUC, respectively, after single dosing (5% and 10%, respectively, after multiple dosing), which are unlikely to be of clinical significance.

A study conducted in healthy elderly male and female subjects showed that the estimated AUC and C_{max} values fall within the same range as those of GERD patients (Study QBE-0037). In addition, an analysis of AUC and C_{max} values from all studies that included elderly subjects showed no statistically significant effect of age on PK. No dosage adjustment of H 199/18 is warranted in elderly patients.

14.6. Pregnant Women and Nursing Mothers

The PK, safety and effectiveness of H 199/18 have not been assessed in pregnant women or nursing mothers.

14. How relevant were the drug-drug interaction studies and were there cases where dosage adjustment is warranted?

15.1. In Vitro Studies

The potential for H 199/18 to inhibit human liver microsomal CYP enzymes in vitro was ranked as follows¹:

CYP 2C9 > CYP 3A4 = CYP 1A2 > CYP 2E1 > CYP 2D6 > CYP 2A6

In vitro studies were performed to evaluate the potential for H 199/18 to inhibit the metabolism of other co-administered drugs. The maximal plasma concentration observed in vivo with the highest proposed H 199/18 dosage (40 mg) after single or multiple dose administration is around 5 μ M, which falls significantly below the K_i values for in vitro inhibition of all CYP isoforms by H 199/18 except for CYP 2C9 and CYP 3A4. This suggested that at therapeutic drug levels, H 199/18 is likely to inhibit to an appreciable extent CYP isozymes 2C9 and 3A4.

Table 5. K_i values for in vitro inhibition of specific CYP isoforms by H 199/18

CYP isoform	K_i (μ M)
CYP 1A2	—
CYP 2C9	—
CYP 2D6	84
CYP 2E1	58
CYP 3A4	—

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¹ The potential for interaction with CYP 2C19 was not assessed due to interference with analytical methodology. However, H 199/18 is known to exhibit significant CYP 2C19 inhibitory activity in vivo based on earlier studies.

15.2. In Vivo Studies

The potential for H 199/18 to inhibit human liver microsomal CYP enzymes in vivo was assessed using known probes, including CYP 3A4 (quinidine, cisapride and clarithromycin), CYP 2C19 (diazepam, phenytoin and warfarin), CYP 1A2 (Caffeine).

The most pronounced drug-drug interaction observed was that with diazepam. However, it is unlikely to be of major clinical relevance. During the course of those studies, the PK of H 199/18 was not affected to any significant extent except when combined with clarithromycin. Thus, the focus of this section will be mostly limited to the impact of the metabolic inhibitory activity of H 199/18 on the PK of other CYP substrates.

15.2.1. Diazepam

A study was conducted to investigate the PK of diazepam, a known CYP 2C19 probe, and the formation of one of its active metabolites, N-desmethyldiazepam, during repeated oral administration H 199/18 in healthy subjects. Either 30 mg H 199/18 solution or placebo was administered once daily for 9 days to 10 male subjects. On day 5, a single dose of 0.1 mg/kg diazepam was administered as a short-term IV infusion. Diazepam AUC increased by 45% while total clearance decreased by the same magnitude, which indicates inhibition of diazepam metabolism by H 199/18 (Study QBE-003).

Another study that evaluated the interaction potential for the 40 mg dose of omeprazole showed an increase in diazepam AUC by 142%. An earlier study investigating the clinical consequences of diazepam-cimetidine PK interaction demonstrated that an increase in the total concentration of total diazepam and desmethyldiazepam by 57% translated into minimal and insignificant changes in clinical effects attributed to diazepam treatment. Thus, H 199/18 (20 mg)-diazepam interaction is unlikely to have any significant clinical relevance.

15.2.2. Phenytoin

A study was conducted to investigate the PK of phenytoin during repeated oral administration H 199/18 in healthy subjects. The steady-state AUC of phenytoin increased by 11% during treatment with H 199/18, while C_{max} was unchanged (Study QBE-0004). An additional study that was conducted to evaluate the potential interaction between H 199/18 and phenytoin in healthy male and female subjects showed that the AUC and C_{max} of phenytoin increased by 13% and 10%, respectively (Study SH-QBE-0032). The H 199/18-phenytoin interaction is unlikely to be of clinical relevance.

15.2.3. Quinidine

A study was conducted to investigate the PK of quinidine and the formation of one of its active metabolites, 3-hydroxyquinidine, during repeated oral administration H 199/18 in healthy subjects. The concomitant administration of H 199/18 with quinidine did not significantly affect the PK of either quinidine or 3-OH-quinidine. Hence, the H

199/18-quinidine interaction is unlikely to be of any clinical relevance (Study QBE-0005).

15.2.4. Amoxicillin and Clarithromycin

A study was conducted to evaluate the potential PK interactions between a 40 mg H 199/18 capsule once daily, 1 g amoxicillin b.i.d. and 500 mg clarithromycin b.i.d. after repeated administration in healthy subjects. The PK of both amoxicillin and clarithromycin after combination treatment were very similar to those of monotherapies. However, the AUC and C_{max} of 14-OH-clarithromycin were 19% and 22% higher, respectively, with combination treatment compared to monotherapy. As for H 199/18, AUC, C_{max} and $t_{1/2}$ were 70%, 18% and 35% higher, respectively after combination treatment. A similar study showed that whereas the PK of clarithromycin and amoxicillin changed little with combination treatment compared to monotherapy, AUC, C_{max} and $t_{1/2}$ of H 199/18 increased by 127%, 39% and 50%, respectively (Study SH-QBE-0040).

15.2.5. Cisapride

A study was conducted to evaluate the potential PK interactions between H 199/18 and cisapride during repeated oral administration in healthy subjects. The AUC and $t_{1/2}$ for cisapride were 32% and 31% larger, respectively, after co-administration with H 199/18 compared to cisapride alone. It is noteworthy that cisapride is not marketed currently in the US (Study QBE-0036).

15.2.6. Warfarin

A study was carried out to investigate the effect of H 199/18 on the steady-state plasma levels and anticoagulant effect of warfarin in patients on warfarin. The mean trough plasma concentration of R-warfarin was increased by 13% during H 199/18 treatment, while that of S-warfarin was unchanged. The H 199/18-R-warfarin interaction is unlikely to be of clinical relevance, since the majority of the anticoagulant activity of warfarin is attributed to the S-enantiomer (Study QBE-0038).

15.2.7. Caffeine

A study was conducted to evaluate the potential for H 199/18 to induce the metabolism of caffeine, a known 1A2 substrate. Earlier studies have shown that omeprazole induces, albeit to a weak extent, CYP 1A2 enzyme activity in vivo. No consistent changes were noted in caffeine metabolism with concomitant H 199/18 administration, which implies that those compounds do not appreciably inhibit CYP 1A2 enzyme. However, it should be noted that large inter-individual variability was observed with the caffeine breath test data, which limits the reliability of the findings (Study QBE-0001).

15.2.8. Oral Contraceptives

Analysis of data extracted from two clinical studies where females on oral contraceptives received H 199/18 showed that AUC and C_{max} of H 199/18 increased by 45% and 15%, respectively. The reliability of those estimates is doubtful since data pooling and cross-study comparisons were employed. In any case, such increases in AUC and C_{max} of H 199/18 are unlikely to have a major clinical relevance.

15.2.9. Other potential drug-drug interactions

- The potential for omeprazole to interact with either metoprolol (CYP 2D6 probe) or ethanol (CYP 2E1 probe) has been assessed in vivo and the results agreed with in vitro findings, which indicate that omeprazole does not interact with either drug to any significant extent.
- Potential drug-drug interactions relating to the effect of H 199/18 on the absorption of several drugs have not been assessed by the sponsor. This is particularly important for drugs such as digoxin, itraconazole and ketoconazole. In one study, concomitant administration of ketoconazole and omeprazole resulted in a reduction in bioavailability and C_{max} of ketoconazole by as much as 80%.

16. Were the dissolution test conditions and specifications appropriately selected to relate to the in vivo conditions for BA and BE?

The proposed dissolution rate test was as follows:

Pre-exposure (Acid stage): Capsule is exposed for 2 hrs to 300 ml of 0.1M HCL/37°C/100 rpm.

Drug Release (buffer stage): In USP apparatus II (paddle), 700 ml of Na_2HPO_4 is added to the medium containing the capsule to give 1000 ml with a pH of 6.8. After 30 min/37°C/100 rpm, the release of H 199/18 is determined by HPLC with UV detection. The proposed dissolution specification mandates a $Q = \text{—}$ for acceptance.

This dissolution method is similar to the dissolution method currently employed for omeprazole. Batch analyses were conducted for \sim batches of H 199/18 delayed-release capsules 10, 20 and 40 mg, which were used in Phase II/III clinical studies, Phase I studies (bioequivalence, bioavailability) and NDA stability studies. All the tested batches met the specifications set earlier.

17. Were the bioanalytical methods utilized in the Clinical pharmacology studies adequately validated?

The bioanalytical methods were specific, precise, sensitive, linear and reproducible.

The analytical assays utilized throughout the Clinical Pharmacology and Biopharmaceutics-related studies

The majority of studies employed _____ method for determination of omeprazole, H199/18 and their metabolites in human plasma. The analytical assay was adequately validated with respect to sensitivity, specificity, precision and reproducibility.

18. Does the proposed labeling language for H 199/18 conform with CPB study findings?

See attachment 2 for the proposed labeling language for H 199/18.

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Individual Study Summary

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Type of Study: Mass Balance

Study SH-QBE-0024 is entitled,

**“PHARMACOKINETICS AND METABOLIC PATTERN OF H 199/18
COMPARED WITH OMEPRAZOLE AFTER SINGLE ORAL
ADMINISTRATION”**

Objectives

1. To study the metabolic pattern, as well as the excretion in urine and feces during a 48 hour period, of H 199/18 and omeprazole in healthy subjects after oral administration of [¹⁴C]-H 199/18 and [¹⁴C]-omeprazole.
2. To compare the metabolic patterns of H 199/18 and omeprazole in extensive and poor metabolizers of omeprazole.

Primary Review Issues

1. How does the pharmacokinetics of H 199/18 compare to that of omeprazole after a single oral administration?
2. How does the metabolic pattern compare between poor and extensive metabolizers after single dose administration of H 199/18 and omeprazole?

Study Design

Open, randomized, cross-over study in healthy subjects

Subjects 6 male subjects (4 EMs & 2 PMs), Age (28.8 yrs) and weight (74.2 kg)

Treatments Subjects were randomized into two treatment groups, where each group received each of the following two treatments in a crossover manner:

- **Treatment A: A single oral dose of 40 mg H 199/18 including 2 MBq H 199/18-¹⁴C**
- **Treatment B: A single oral dose of 40 mg omeprazole including 2 MBq omeprazole-¹⁴C**

Five min prior to dose administration, 50 ml of buffer solution were administered to each subject. Directly after each oral dose, 100 ml of sodium bicarbonate buffer solution was administered to each subject. In addition, 50 ml of the buffer solution was administered 10, 20 and 30 min after drug ingestion to prevent drug degradation of the acid-labile H 199/18.

Washout Period at least 2 weeks

Plasma Sampling Samples were collected for determination of H 199/18 in plasma, urine and feces at the following time points:

- **Plasma:** At 0 (pre-dose), 5, 10, 15, 20, 30 min, and 1, 2, 3, 4, 6, 8, 12 and 24 hrs post-dose
- **Urine:** At the intervals 0-2, 2-4, 4-8, 8-12, 12-24, and 24-48 hrs post-dose. The plastic bottles used for collection of urine samples contained aq. sodium bicarbonate (2.5 ml of 1 mol/L per collection hour)
- **Feces:** At the intervals the day before drug administration, 0-24 and 24-48 hrs post-dose

Analytical Assay

The assay consisted of _____
 Plasma and urine samples were analyzed according to methods _____
 _____ respectively.

Pharmacokinetics

The following pharmacokinetic parameters were determined for H 199/18 and omeprazole using non-compartmental analysis: T_{max} , C_{max} , $t_{1/2}$, AUC_{0-t} , and $AUC_{0-\infty}$. In addition, recovery and excretion routes of total radioactivity were determined as % administered dose.

Results

Table 1. Estimates for the mean primary PK parameters (\pm S.D.) for H 199/18 and omeprazole after administration of treatments A and B

	H 199/18	Omeprazole
PMs		
AUC ($\mu\text{mol}\cdot\text{h/L}$)	17.03 (0.40)	20.74 (0.80)
C_{max} ($\mu\text{mol/L}$)	7.95 (1.91)	7.52 (0.99)
$t_{1/2}$ (hr)	1.87 (0.04)	2.16 (0.25)
T_{max} (hr)	0.29 (0.06)	0.34 (0.23)
AUC of total radioactivity ($\mu\text{mol}\cdot\text{h/L}$)	74.10 (1.97)	51.33 (1.84)
$t_{1/2}$ of total radioactivity (hr)	8.88 (0.33)	6.14 (0.63)
EMs		
AUC ($\mu\text{mol}\cdot\text{h/L}$)	5.95 (2.54)	3.89 (2.00)
C_{max} ($\mu\text{mol/L}$)	5.64 (1.85)	5.17 (2.93)
$t_{1/2}$ (hr)	0.89 (0.32)	0.69 (0.19)
T_{max} (hr)	0.29 (0.05)	0.25 (0.17)
AUC of total radioactivity ($\mu\text{mol}\cdot\text{h/L}$)	25.61 (6.74)	14.99 (3.73)
$t_{1/2}$ of total radioactivity (hr)	3.99 (1.23)	2.25 (0.31)

Table 2. Cumulative excretion of total radioactivity (% dose) in EMs after administration of treatment A

	(0-2) hr	(0-4) hr	(0-8) hr	(0-12) hr	(0-24) hr	(0-48) hr
Urine	33.3	50.3	62.0	67.5	73.8	77.0
Feces	---	---	---	---	5.0	18.5
Total	---	---	---	---	78.7	95.5

Table 3. Cumulative excretion of total radioactivity (% dose) in PMs after administration of treatment A

	(0-2) hr	(0-4) hr	(0-8) hr	(0-12) hr	(0-24) hr	(0-48) hr
Urine	15.5	29.5	45.0	53.5	65.5	72.5
Feces	---	---	---	---	14.0	22.0
Total	---	---	---	---	79.5	94.5

As shown in Table 3, oral doses of H 199/18 were almost completely excreted in urine and feces within 48 hrs, with greater than 70% of the dose being excreted in urine. In addition, the metabolism of H 199/18 or omeprazole was extensive with less than 1% of the parent compound detected in each sample and more than 20 radiolabelled compounds separated. Of the radiolabelled compounds separated, nine major metabolites were identified in urine that were formed via hydroxylation of the 5-methylpyridine group and further oxidation to the corresponding carboxylic acid, and demethylation or hydroxylation of the benzimidazole moiety, followed by conjugation with glucuronic acid.

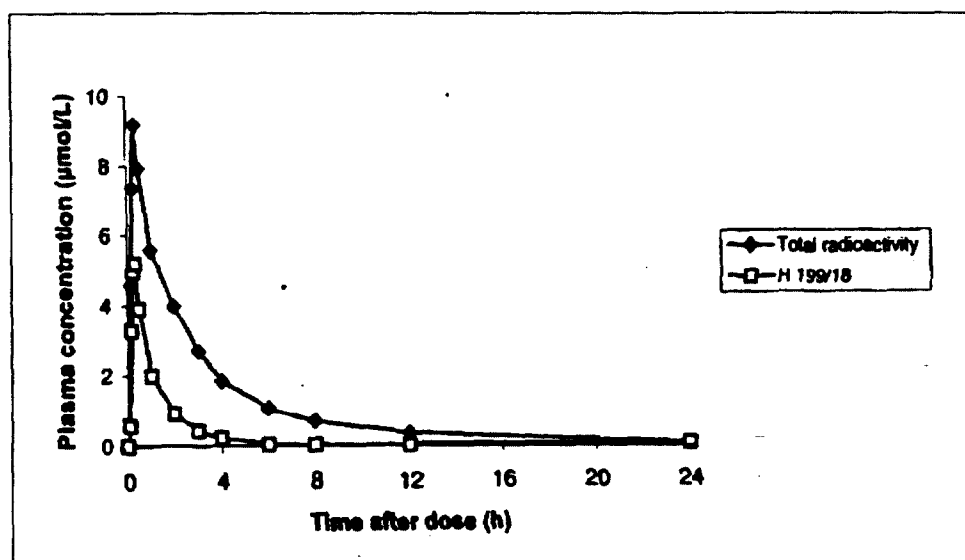


Fig. 1. Mean plasma concentrations of H 199/18 in EMs after administration of a single oral dose of 40 mg H 199/18 including 2 MBq ¹⁴C-H 199/18

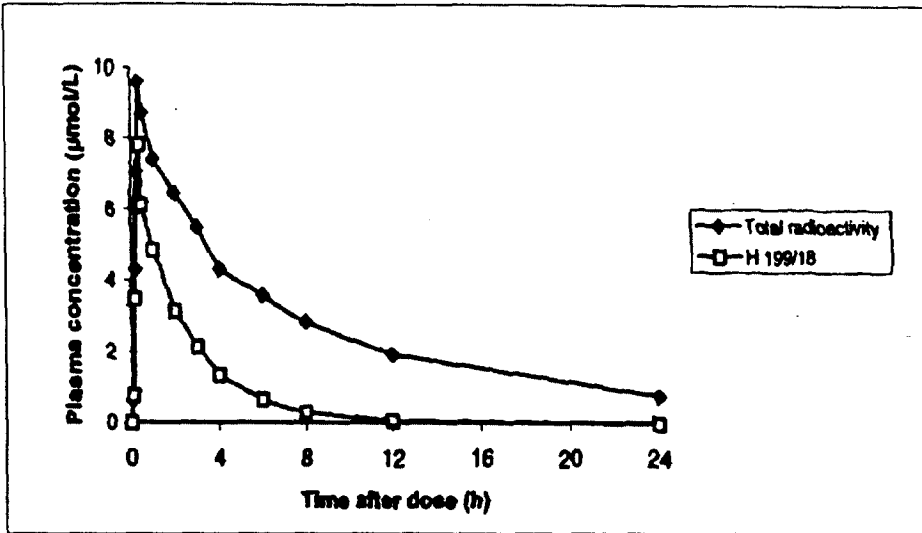


Fig. 2. Mean plasma concentrations of H 199/18 in PMs after administration of a single oral dose of 40 mg H 199/18 including 2 MBq ¹⁴C-H 199/18

Reviewer's Comments

- *Omeprazole and H 199/18 demonstrate similar elimination patterns in humans, with the oral dose undergoing extensive hepatic metabolism followed by excretion of most of the dose (> 70%) in urine.*
- *Greater disparity exists between PMs and EMs with administration of an oral dose of omeprazole compared to that of H 199/18 (Table 1). It should also be pointed out that the main routes of metabolism of H 199/18 and omeprazole did not significantly differ between the two genotypic subsets of subjects and the differences in metabolism were mainly quantitative.*

NDA: 21-153/ Study 24113

Study Date: Nov 1998

Type of Study: Identification of *In Vitro* Metabolic Enzymes

Study 24113 is entitled,

“IDENTIFICATION OF THE HUMAN LIVER CYP ENZYMES INVOLVED IN THE METABOLISM OF THE ENANTIOMERS OF OMEPAZOLE”.

Objectives

To identify the metabolic route for omeprazole’s enantiomers using human liver microsomes.

Primary Review Issue

What is the metabolic route for the enantiomers of omeprazole in man?

Study Design

A correlation study was conducted using liver microsomes from 10 different human livers to establish the linearity of the formation rate of the metabolites of S-omeprazole and R-omeprazole with respect to protein concentration and time. Based on these results, the kinetic studies were performed using cDNA-expressed human P450 isoforms. Five different substrate concentrations, ranging from 20-500 μM (2D6, 2A6 and 3A4) or from 10-200 μM (2C9-arg) or from 5-200 μM (2C19), were used in these experiments. Due to difficulties in the evaluation of the chromatograms of the sulphone metabolite at high concentrations of R-omeprazole, the formation rate of this metabolite by CYP3A4 was only studied in the concentration range 20-100 μM .

Results and Conclusions

Table 1. Kinetic parameters (\pm SE) of the formation of metabolites from S-omeprazole in microsomes prepared from a human lymphoblastoid cell line

	Metabolite	2C19	2C9-arg	3A4	2A6	2D6-val
V_{\max} (nmol/min/nmol P450)	Sulphone	---	---	13.3 \pm 0.53	---	---
	5-O-desmethyl	2.35 \pm 0.15	0.77 \pm 0.40	0.74 \pm 0.24	---	NE
	Hydroxy	0.99 \pm 0.10	1.71 \pm 0.69	2.13 \pm 0.80	1.11 \pm 1.16	NE
K_m ($\mu\text{mol/L}$)	Sulphone	---	---	83.0 \pm 8.80	---	---
	5-O-desmethyl	1.59 \pm 0.99	107 \pm 121	262 \pm 162	---	NE
	Hydroxy	6.01 \pm 2.80	209 \pm 140	367 \pm 235	1000 \pm 1440	NE
CL_{int} ($\mu\text{L/min/nmol}$ P450)	Sulphone	---	---	160 \pm 11.6	---	---
	5-O-desmethyl	1479 \pm 853	7.20 \pm 4.60	2.80 \pm 0.90	---	3.10 \pm 0.30
	Hydroxy	165 \pm 67.0	8.10 \pm 2.30	5.80 \pm 1.70	1.11	6.50 \pm 0.30

NE: Not estimated

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Table 2. Kinetic parameters (\pm SE) of the formation of metabolites from R-omeprazole in microsomes prepared from a human lymphoblastoid cell line

	Metabolite	2C19	2C9-arg	3A4	2A6	2D6-val
V_{max} (nmol/min/nmol P450)	Sulphone	---	---	1.30 \pm 0.29	---	---
	5-O-desmethyl	0.60 \pm 0.05	---	---	---	NE
	Hydroxy	12.9 \pm 0.80	---	5.95 \pm 0.80	---	NE
K_m (μ mol/L)	Sulphone	---	---	82.4 \pm 33.6	---	---
	5-O-desmethyl	4.48 \pm 2.10	---	---	---	NE
	Hydroxy	3.99 \pm 1.46	---	316 \pm 82	---	NE
CL_{int} (μ l/min/nmol P450)	Sulphone	---	---	15.7 \pm 3.09	---	---
	5-O-desmethyl	133 \pm 56	---	---	---	4.2 \pm 0.40
	Hydroxy	3233 \pm 1053	---	18.8 \pm 2.6	---	5.7 \pm 0.40

NE: Not estimated

It is noteworthy that earlier in vitro studies have identified CYP 2C19 and CYP 3A4 isoymes as the primary metabolic enzymes responsible for the formation of the hydroxy and sulphone metabolites, respectively¹.

In summary, the formation CL_{int} of the hydroxy metabolite from S-omeprazole was more than 10 times lower than that of R-omeprazole, whereas the CL_{int} of the sulfone and 5-O-desmethyl metabolites for S-omeprazole were more than 10 times higher than those of R-omeprazole. Altogether, this data suggests that CYP 2C19 plays a much bigger role in the metabolism of R-omeprazole compared to S-omeprazole. The sum of the formation CL_{int} of all three metabolites was 14.6 and 42.5, respectively, for S- and R-omeprazole, which suggests that S-omeprazole is cleared more slowly than R-omeprazole in the human liver.

NDA: 21-153/ Study 24049

Study Date: Nov 1998

Type of Study: In Vitro Protein Binding

Study 24049 is entitled,

“IN VITRO PROTEIN BINDING OF OMEPRAZOLE, H 199/18 AND H 199/19 IN PLASMA FROM HUMANS”.

Objectives

To determine the protein binding of omeprazole and its enantiomers, H 199/18 and H 199/19, in human plasma.

¹ Andersson et al. *Identification of human liver cytochrome P450 isoforms mediating omeprazole metabolism.* Br J Clin Pharmacol. 1993; 36:521-530.

Primary Review Issue

How big a fraction of each of omeprazole and its enantiomers is bound to plasma proteins ?

Study Design

Fresh plasma was obtained from 6 drug-free healthy humans (3 males and 3 females). The plasma from each human was used for the three compounds at two concentrations, 2 and 20 µmol/L, which were selected to cover the relevant therapeutic plasma concentrations of the tested compounds. The plasma protein binding of omeprazole and its enantiomers, H 199/18 and H 199/19, was determined by _____

The concentrations of omeprazole, H 199/18, and H 199/19 were determined by _____
_____ LOQ was _____ for the 1:1 mixture of bicarbonate buffer and plasma, and 50 nmol/L for plasma.

The percentage bound to plasma proteins was calculated as follows:

$$\%Bound = \left(1 - \frac{\left(\frac{C_u}{C_{tot}} \right)_{plasma}}{\left(\frac{C_u}{C_{tot}} \right)_{buffer}} \right) \cdot 100\%$$

Where C_u is the concentration of the compound in the _____ and C_{tot} is the total concentration of the compound in plasma and buffer, respectively.

Results

Table 1. Mean (\pm S.D.) protein binding of omeprazole and its enantiomers at two concentrations in plasma from **male** humans

	% Bound at 2 µmol/L	% Bound at 20 µmol/L
<i>Omeprazole</i>	96.8 (0.1)	97.1 (0.4)
H 199/18	97.2 (0.2)	97.3 (0.3)
H 199/19	96.9 (0.2)	97.1 (0.6)

Table 2. Mean (\pm S.D.) protein binding of omeprazole and its enantiomers at two concentrations in plasma from female humans

	% Bound at 2 $\mu\text{mol/L}$	% Bound at 20 $\mu\text{mol/L}$
<i>Omeprazole</i>	96.8 (0.5)	97.1 (0.4)
H 199/18	97.0 (0.7)	97.1 (0.5)
H 199/19	96.7 (0.7)	96.5 (0.7)

Reviewer's Comments

The protein binding of omeprazole and its enantiomers, H 199/18 and H 199/19, in human plasma is high (97%) and appears to be independent of gender and concentration within the studied range (2-20 $\mu\text{mol/L}$).

NDA: 21-153/ Studies SH-QBE-0001 & SH-QBE-0027

Study Date: Feb 1997 & Dec 1997

Type of Study: Potential for Inversion of H 199/18 and H 199/19

Study SH-QBE-0001 is entitled,

“INVESTIGATION OF ANY INVERSION OF H 199/18 SODIUM AND H 199/19 SODIUM IN HEALTHY SUBJECTS”

Study SH-QBE-0027 is entitled,

“INVESTIGATION OF ANY INVERSION OF H 199/18 IN HEALTHY MALE SUBJECTS”

Objectives

To investigate the potential inversion of H 199/18 and H 199/19 in healthy human subjects. This is important for two reasons:

- For omeprazole and its enantiomers, whereas the pharmacodynamic effect (inhibition of gastric acid secretion) is not subject to stereoselectivity based on in vitro studies, the pharmacokinetics, such as metabolism, are highly influenced by stereoselectivity. Hence, it is quite important to determine whether any inversion of the enantiomers takes place.
- From the analytical perspective, enantioselective assays are generally less robust and less sensitive compared to achiral assays. Therefore, if it is established that negligible inversion occurs, it would be of significant advantage to utilize an achiral assay.

Primary Review Issue

Does Significant inversion of H 199/18 or H 199/19 take place in humans?

Study SH-QBE-0001

Study Design

Two groups of extensive metabolizers (EMs) and poor metabolizers (PMs) were selected to participate in the study. EMs were given an oral dose of 15 mg of H 199/18 sodium or H 199/19 sodium on separate occasions. PMs were given an oral dose of 60 mg of H 199/18 sodium or H 199/19 sodium on separate occasions.

Samples from 3 randomly selected EMs and 3 randomly selected PMs were drawn. Samples containing peak concentrations of H 199/18 and H 199/19, as well as samples taken later after dosing were selected for enantioselective analysis. The enantioselective analytical method consisted of _____

_____ The LOQ for H 199/18 and H 199/19 was _____ nmol/L, respectively.

Results

In EMs, plasma levels of H 199/18 and H 199/19 were mostly below the limit of detection. Hence, the inversion of either of the enantiomers could not be determined in any of the subjects.

In PMs, the concentration of the antipode in all the samples was less than 4% of the sum of the enantiomers, except for three late samples (10-13%), where the assay was claimed to be less reliable due to interference with an endogenous compound.

Reviewer's Comments

- *No valid conclusions can be drawn from the data for the EMs due to inability of the analytical assay to adequately measure low plasma concentrations of the antipodes. However, minimal inversion (< 4%) seems to take place in PMs.*

Study SH-QBE-0027

Study Design

A single 40 mg dose of H 199/18 was administered to 8 healthy male subjects (20-50 years old) and blood samples were drawn before and at 0.5, 0.75, 1, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 7 and 8 hours post-dose. The samples were subsequently quantified according to method _____

Non-compartmental analysis was utilized to calculate C_{max} and AUC_{0-t} for both H 199/18 and H 199/19. The estimated ratio of the true geometric means of AUC_{0-t} for H 199/19 to AUC_{0-t} for H 199/18 together with the corresponding 95% confidence interval was calculated.

Results

The degree of inversion based on the ratio of the true geometric means of AUC_{0-t} for H 199/19 and H 199/18 was estimated to be 0.4% and 2.1% based on the “most realistic” and the “most conservative” approaches.

Reviewer's Comments

The study indicates that H 199/18 is optically-stable and the degree of inversion seems to be negligible.

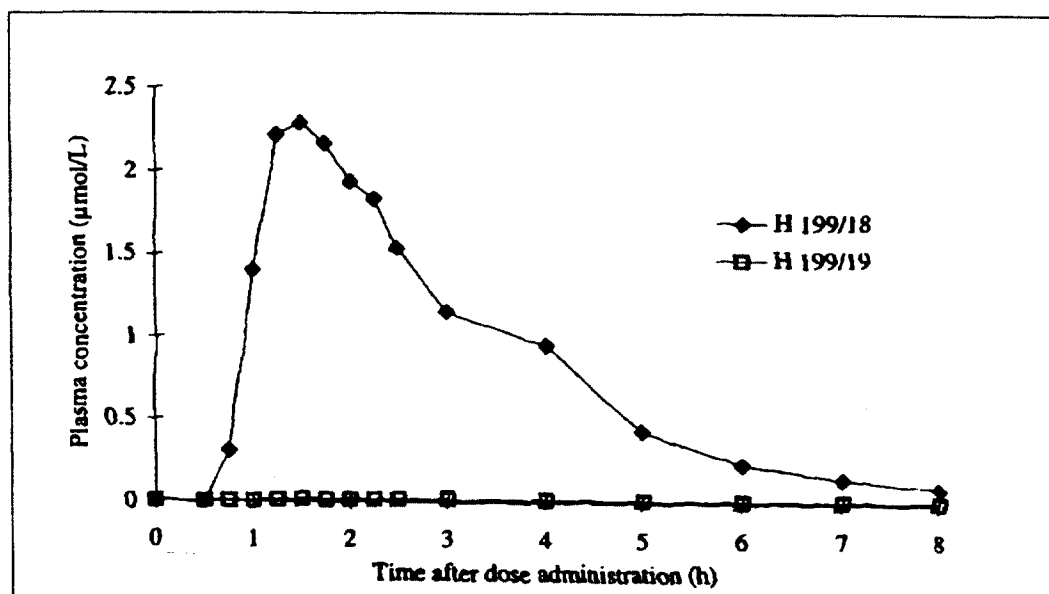


Fig. 1. Mean plasma concentrations of H 199/18 and H 199/19 over time after administration of a 40 mg oral dose of H 199/18.

NDA: 21-153/ Studies SH-QBE-0006 & SH-QBE-0045

Study Date: Aug-Sep 1995 & May-Jul 1998

Type of Study: Single and Multiple Dose PK

Study SH-QBE-0006 is entitled,

“PHARMACOKINETIC STUDY OF H 199/18 SODIUM AFTER ORAL AND INTRAVENOUS ADMINISTRATION OF SINGLE AND REPEATED DOSES IN HEALTHY SUBJECTS”

Study SH-QBE-0045 is entitled,

“A PHARMACOKINETIC STUDY OF H 199/18 AFTER INTRAVENOUS AND ORAL ADMINISTRATION OF SINGLE AND REPEATED DOSES IN HEALTHY SUBJECTS”

Objectives

To characterize the pharmacokinetics of H 199/18 after oral and IV administration of single and multiple doses to healthy subjects

Primary Review Issue

What is the pharmacokinetic profile of H 199/18 after oral and IV administration of single and multiple doses to healthy subjects?

Study SH-QBE-0006

Study Design

Open, two-period study in healthy subjects

Subjects 16 subjects

Key Inclusion

Criteria Age 20-40 yrs, wt within 66-86 kg
Characterized as rapid metabolizers of
 omeprazole

Key Exclusion

Criteria Concomitant medication
History of cardiac, renal, hepatic or significant GI diseases

Treatments

One single 20 mg dose of H 199/18 was administered IV on day 1. After a washout period, repeated daily oral dosing followed for 5 days. On the last day after the last oral dose, a second IV dose was administered. Directly after each 20 mg oral dose, 100 ml of sodium bicarbonate buffer solution was administered to each subject. In addition, 50 ml of the buffer solution was administered 5 min prior to and 10, 20 and 30 min after drug ingestion to prevent drug degradation of the acid-labile H 199/18. The same procedure for buffer addition was followed for the IV treatments, so as to get identical experimental conditions to the oral treatment.

Washout Period 5-10 days

Plasma Sampling

Blood samples were collected for determination of H 199/18 in plasma at the following time points after each treatment:
At -5 (pre-dose), 5, 10, 15, 20, 30, and 45 min, 1, 1.5, 2, 3, 4, 6, 7, 8, 10 and 12 hrs post-dose

Pharmacokinetics

The following pharmacokinetic parameters were determined for H 199/18: T_{max} , C_{max} , K_e , AUC_{0-t} , $AUC_{0-\infty}$, and $t_{1/2}$, CL , V_{ss} , F_{Day1} and F_{Day5} .

Results

Table 1. Estimates for the true ratio between PK parameters at day 1 and day 5 during oral administration of H 199/18

	AUC ($\mu\text{mol}\cdot\text{hr}/\text{L}$)	C_{max} (L/hr)	F
Day 1	1.34	1.86	0.50
Day 5	2.55	2.65	0.68
Day 5/Day 1	1.90	1.43	1.35

Table 2. Estimates for the true ratio between PK parameters at day 1 and day 5 during IV administration of H 199/18

	C_{max} ($\mu\text{mol}/\text{L}$)	CL ($\mu\text{mol}/\text{L}$)
First Dose	2.51	21.7
Second Dose	2.67	15.5
Dose 1/Dose 2	1.07	0.71

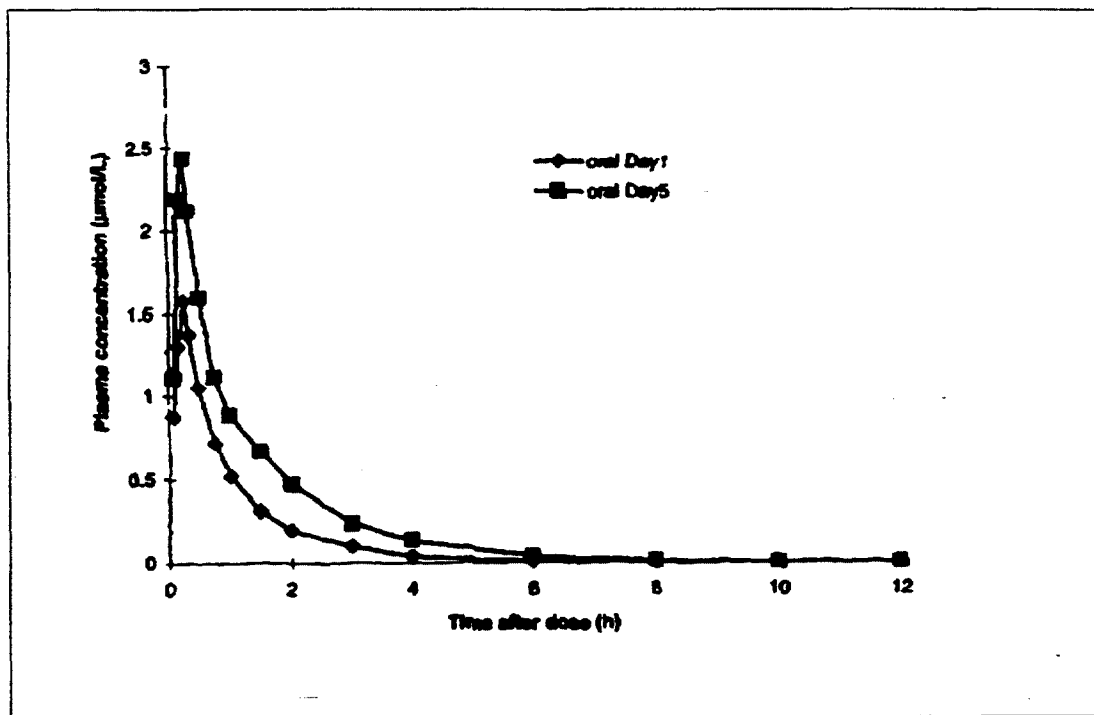


Fig. 1. Mean plasma concentration-time profile of H 199/18 after oral administration

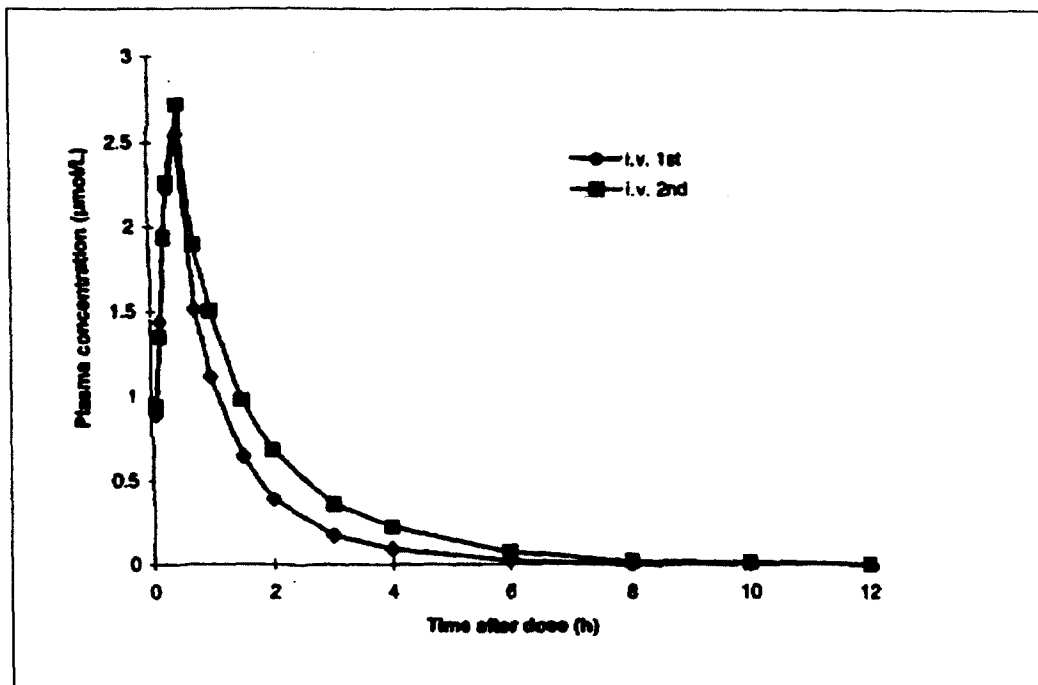


Fig. 2. Mean plasma concentration-time profile of H 199/18 after IV administration

Reviewer's Comments

- A significant reduction (~30%) is apparent in total body clearance after both IV and oral¹ multiple dose administration of H 199/18. Concurrently, C_{max} and AUC estimated after multiple dose administration of H 199/18 increased by 43% and 90%, respectively. Those changes in the PK parameters of H 199/18 after multiple dose administration suggest time-dependent changes.

Study SH-QBE-0045

The study design was practically identical to that of study SH-QBE-0006, with the exception that the subject population was made up of 3 groups of 8 subjects each: males, females on oral contraceptives and females not using oral contraceptives.

An additional objective of this study was to assess the potential influence of gender and concomitant use of oral contraceptives on the PK of H 199/18.

Results

¹ Total clearance after oral administration was estimated based on the following equation: $CL = F \cdot D / AUC$

Table 3. Geometric means and ratios of geometric means for the major PK parameters following single and repeated oral and IV administration of 40 mg H 199/18 to healthy male and female subjects

PK Parameter	Estimated Geometric Mean
F (%)	
Day 1	63.59
Day 5	88.89
Day 5/Day 1	1.40
AUC (oral, $\mu\text{mol}\cdot\text{hr}/\text{L}$)	
Day 1	4.32
Day 5	11.21
Day 5/Day 1	2.59
C_{max} (oral, $\mu\text{mol}/\text{L}$)	
Day 1	2.38
Day 5	4.64
Day 5/Day 1	1.95
$t_{1/2}$ (oral, hr)	
Day 1	0.85
Day 5	1.25
Day 5/Day 1	1.48
CL (IV, L/hr)	
Day 1	17.05
Day 5	9.18
Day 5/Day 1	0.54
V_{ss} (IV, L/kg)	
Day 1	0.25
Day 5	0.22
Day 5/Day 1	0.87

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Reviewer's Comments

- *Total clearance of H 199/18 was almost halved by day 5 of dosing relative to day 1. In addition, AUC increased by more than 2.5 fold by day 5, which could be explained fully by the reduction in clearance paralleled by an increased bioavailability of H 199/18 with multiple dosing. Overall, this seems to conform to results observed in study SH-QBE-0006.*
- *There seems to be good agreement between the major PK parameters calculated for males across studies except for AUC (oral), which is estimated in study SH-QBE-0045 to be more than double that in SH-QBE-0006.*
- *When comparing females not on oral contraceptives with males on the major PK parameters after administration of a single dose of H 199/18, it is apparent that females have significantly lower CL and higher F values compared to males, which is thought to contribute to a higher exposure in females. This trend is still visible after administration of multiple doses of H 199/18. However, the differences in PK parameters between males and females are significantly reduced, probably due to time-dependent changes in PK (i.e.-auto-inhibition of metabolism). Literature reports suggest that the levels of the primary metabolizing enzyme for H 199/18, CYP 2C19, are higher in men than women, which may explain the elevated levels of H 199/18 in women compared to men¹.*
- *Similar estimates of the PK parameters were observed for both females using and females not using oral contraceptives, which indicates that oral contraceptives have little interaction potential with H 199/18.*

**NDA: 21-153/ Studies SH-QBE-0002 &
SH-QBE-0008**

**Study Date: Jan-Jul 1995 &
Mar-Jun 1996**

Type of Study: Dose-Response

Study SH-QBE-0002 is entitled,

“DOSE-RESPONSE STUDY OF H 199/18 SODIUM ON PENTAGASTRIN-STIMULATED GASTRIC ACID SECRETION IN HEALTHY SUBJECTS”

Study SH-QBE-0008 is entitled,

“COMPARATIVE STUDY ON 20 AND 40 mg H 199/18 AND 20 mg OMEPRAZOLE WITH REGARD TO EFFECT ON 24-HOUR INTRAGASTRIC pH”

¹ Hooper WD, Qing M-S. *The influence of age and gender on the stereoselective metabolism and pharmacokinetics of mephobarbital in humans.* Clin. Pharmacol. Ther. 1990; 48: 633-40.

Primary Review Issue

Is there a PK/PD relationship for the effect of H 199/18 on gastric acid secretion?

Study SH-QBE-0002

Objectives

- To study the effect of single and multiple dose (once daily for 5 days) administration of 5, 10 and 20 mg H 199/18 and 20 mg omeprazole, respectively, on pentagastrin-stimulated gastric acid secretion in healthy subjects.
- To evaluate the PK after single and multiple dose administration of 5, 10 and 20 mg H 199/18 and 20 mg omeprazole, respectively.

Study Design

Open, randomized, cross-over study in healthy subjects

<u>Subjects</u>	12 male subjects (age 20-40 yrs)
<u>Treatments</u>	Subjects were randomized to receive each of the following 4 treatment groups once daily over a 5-day period: 5, 10 and 20 mg H 199/18 oral solutions and 20 mg omeprazole enteric-coated pellet formulation
<u>Washout Period</u>	At least 2 weeks
<u>PK Sampling</u>	Samples were collected for determination of H 199/18 in plasma before and at the following time points postdose: 0.25, 0.5, 0.75, 1, 2, 3, 4 and 6 hrs
<u>Gastric Secretion Test</u>	After two 15-min collections of basal secretion, pentagastrin (90 µg/hr) was administered IV and stimulated gastric acid secretion was collected for another four 15-min periods.
<u>Analytical Assay</u>	The assay consisted of _____ Plasma samples were analyzed according to methods _____ _____ respectively.

Pharmacokinetics/Pharmacodynamics

The following pharmacokinetic parameters were estimated using non-compartmental analysis: t_{max} , C_{max} , K_e , AUC_{0-t} , $AUC_{0-\infty}$, and $t_{1/2}$.

The maximum acid response to pentagastrin stimulation was measured as peak acid output (PAO), calculated as the sum of the two highest consecutive 15-min samples multiplied by two and expressed as mmol/L.

The % Change in PAO after drug intake was calculated relative to the control acid secretion test before drug intake.

Results

Table 1. Summary of the mean primary PK and PD parameters for each treatment

Treatment		AUC _{0-t} ($\mu\text{mol}\cdot\text{h/L}$)	% Inhibition of PAO
Omeprazole 20 mg	Day 1	1.25	35.4
	Day 5	1.86	78.7
	Day 5/day 1	1.49	43.3
H 199/18 5 mg	Day 1	0.29	14.6
	Day 5	0.33	27.8
	Day 5/day 1	1.14	13.2
H 199/18 10 mg	Day 1	0.65	29.2
	Day 5	0.98	62.1
	Day 5/day 1	1.51	32.9
H 199/18 20 mg	Day 1	1.47	45.7
	Day 5	3.10	89.9
	Day 5/day 1	2.11	44.1

- Dose proportionality was noted for the primary PK parameters of H 199/18, C_{max} and AUC_{0-t} , at the evaluated dose range of 5-20 mg. However, higher values were attained after 5 days of dosing, likely due to time-dependent changes in PK.

Reviewer's Comments

- *The antisecretory effect of H 199/18 was dose dependent with an increased effect upon repeated daily dosing up to the 20 mg dose. Upon closer inspection, the % inhibition of pentagastrin-stimulated acid secretion showed good correlation with AUC of H 199/18, with a lower AUC needed for maximal inhibition of acid secretion on day 5 relative to day 1. This may be related to the cumulative effect of H 199/18 on the inhibition of proton pumps.*

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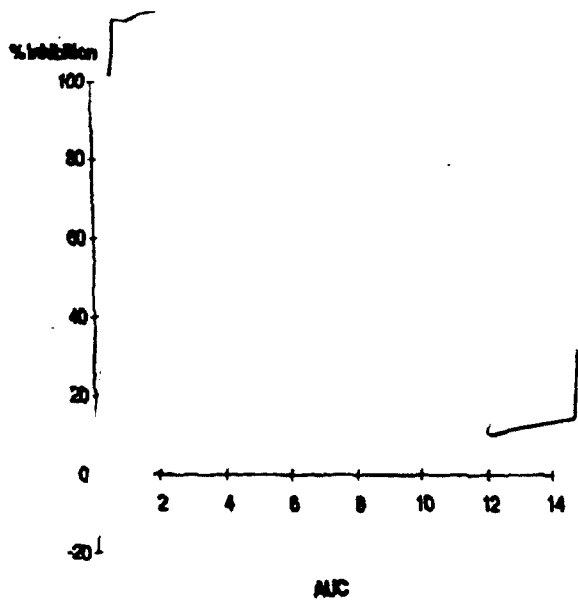


Figure 4. Inhibition (%) of pentagastrin stimulated acid output vs. AUC following administration of 5, 10 and 20 mg H 199/18 and 20 mg omeprazole respectively on day 1.

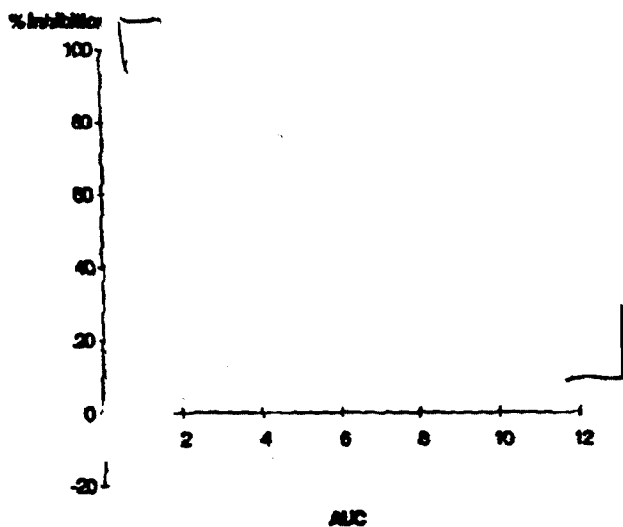


Figure 5. Inhibition (%) of pentagastrin stimulated acid output vs. AUC following administration of 5, 10 and 20 mg H 199/18 and 20 mg omeprazole respectively on day 5.

Study SH-QBE-0008

Objectives

- To compare H 199/18 20 mg with omeprazole 20 mg with respect to their effects on intragastric pH in patients referred for investigation of or with established GERD.
- To compare H 199/18 40 mg with H 199/18 20 mg and with omeprazole 20 mg with respect to their effects on intragastric pH, and to study the PK of H 199/18 and omeprazole. In addition, the bioavailability of the 20 mg dosage forms of H 199/18 and omeprazole will be compared.

Study Design

Double-blind, randomized, three-way cross-over study in patients.

Subjects 36 subjects (15 males and 21 females, age 45.2 yrs)

Treatments Subjects were randomized to receive each of the following 3 treatment groups once daily over a 5-day period: 20 and 40 mg H 199/18 capsules and 20 mg omeprazole enteric-coated capsule formulation.

Washout Period at least 2 weeks

PK Sampling Samples were collected for determination of H 199/18 in plasma before and at the following time points postdose: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 8 hrs

Intragastric pH Test After two 15-min collections of basal secretion, pentagastrin (90 µg/hr) was administered IV and stimulated gastric acid secretion was collected for another four 15-min periods.

Analytical Assay The assay consisted of _____
Plasma samples were analyzed according to methods _____
determination of H 199/18 and omeprazole (LOQ = _____)

Pharmacokinetics/Pharmacodynamics

The following pharmacokinetic parameters were estimated using non-compartmental analysis: t_{max} , C_{max} , K_e , AUC_{0-t} , $AUC_{0-\infty}$, and $t_{1/2}$.

The maximum acid response to pentagastrin stimulation was measured as peak acid output (PAO), calculated as the sum of the two highest consecutive 15-min samples multiplied by two and expressed as mmol/L.

The % Change in PAO after drug intake was calculated relative to the control acid secretion test before drug intake.

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Results

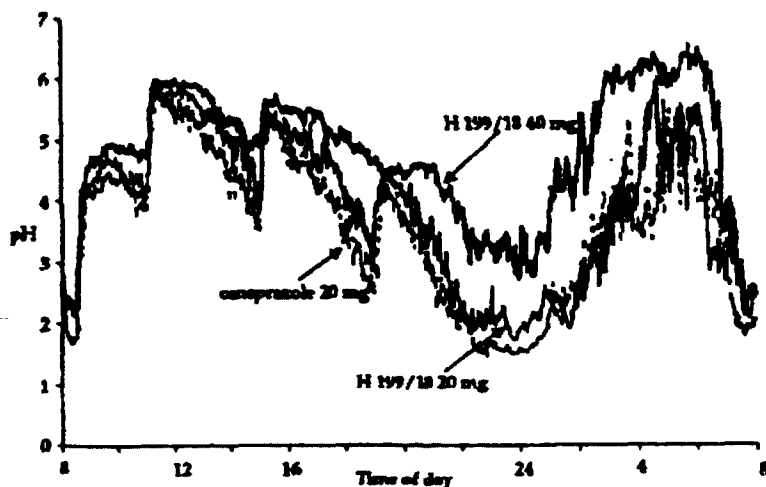
Table 2. Summary of the mean primary PK and PD parameters for each treatment

PK/PD Parameter	Omeprazole 20 mg	H 199/18 20 mg	H 199/18 40 mg
PK			
C _{max} (μmol/L)	1.41	2.42	5.13
t _{max} (hr)	1.0	1.0	1.2
t _{1/2} (hr)	1.0	1.3	1.6
AUC ₀₋₂₄ (μmol·h/L)	2.34	4.18	12.64
PD			
% time at pH>4	43.72 (36.74-50.71) [†]	53.01 (46.03-59.99) [†]	69.83 (62.85-76.81) [†]
Median 24-hr pH	3.58 (3.22-3.94) [†]	4.14 (3.78-4.50) [†]	4.88 (4.52-5.24) [†]

[†] 95% Confidence interval.

Reviewer's Comments

• Based on the PD markers utilized as measures of the effectiveness of each of the treatments in reducing intragastric acidity, there seems to be a relationship between exposure (AUC) of H 199/18 and effect (reduction in intragastric acidity). H 199/18 40 mg, as might be expected, is superior to the 20 mg dose of both H 199/18 and omeprazole. Despite a trend for an enhanced effectiveness by H 199/18 20 mg compared to omeprazole 20 mg, the confidence intervals of both treatments significantly overlap, thus obscuring interpretation of the inter-treatment differences. Therefore, it may not be concluded based on the results of the current study that H 199/18 is more effective than omeprazole at a dose of 20 mg.



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Figure 2. Median 24-hour pH-profiles in patients with symptomatic GORD, n=36.

Type of Study: Relative Bioavailability of H 199/18 Capsules

Study SH-QBE-0007 is entitled,

“RELATIVE BIOAVAILABILITY OF H 199/18 AFTER ADMINISTRATION OF REPEATED DOSES OF TWO FORMULATIONS IN HEALTHY SUBJECTS”.

Objectives

To compare the bioavailability of a capsule formulation, containing enteric coated granules of H 199/18 to that of an oral solution of H 199/18 in healthy subjects.

Primary Review Issue

How much H 199/18 is bioavailable after oral administration of a capsule formulation ?

Study Design

Twelve healthy male subjects (age 20-40 years, wt 66-86 kg) received 20 mg H 199/18 either as solution or a capsule for 5 days in an open, two-way crossover fashion separated by a washout period of at least 14 days. In each treatment period, blood samples were drawn for determination of H 199/18 before and at 5, 10, 15, 20, 30, 45, min and 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hrs post-dose.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method (LOQ = nmol/L).

Pharmacokinetics

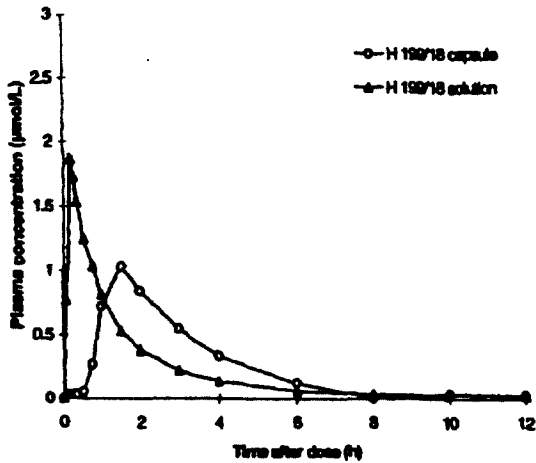
The following pharmacokinetic parameters were estimated for H 199/18 using non-compartmental analysis: t_{max} , C_{max} and $AUC_{0-\infty}$.

Results

Table 1. Estimates of means of the primary PK parameters after administration of 20 mg H 199/18 as either capsule or oral solution for 5 days

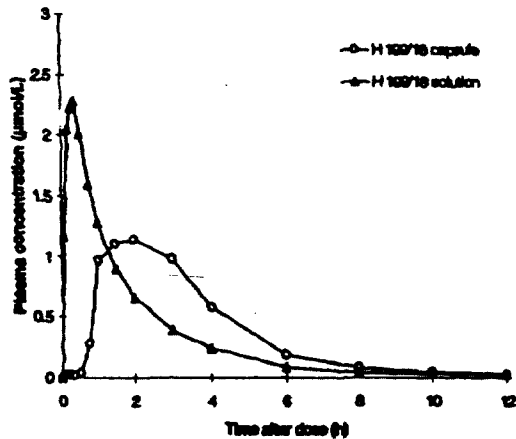
PK Parameter	H 199/18 Capsule	H 199/18 Solution
Day 1		
C_{max}	1.04	1.92
AUC	1.79	1.82
Day 5		
C_{max}	1.64	2.62
AUC	3.27	3.19

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Figure 2. Mean plasma concentration following administration of 20 mg H 199/18 orally as a capsule or as a solution on day 1.



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Figure 3. Mean plasma concentration following administration of 20 mg H 199/18 orally as a capsule or as a solution on day 5.

Reviewer's Comments

- The relative bioavailability of the capsule formulation was 99% on day 1 and 103% on day 5, which suggests that there were no-time dependent changes in bioavailability at an H 199/18 dose of 20 mg.

NDA: 21-153/ Study SH-QBE-0023

Study Date: Sep-Oct 1997

Type of Study: Comparative Bioavailability of H 199/18 — Tablets

Study SH-QBE-0023 is entitled,

“A SINGLE-DOSE BIOAVAILABILITY STUDY IN HEALTHY SUBJECTS COMPARING TWO DIFFERENT TABLET FORMULATIONS OF H 199/18 WITH A CAPSULE OF H 199/18”.

Objectives

To determine the bioavailability of two _____) tablets of H 199/18 with different compositions relative to that of a capsule of H 199/18 (used in the clinical trials) after single-dose administration of equivalent doses to healthy subjects.

Primary Review Issue

How much H 199/18 is bioavailable after oral administration of two _____, tablets relative to the capsule formulation ?

Study Design

Eighteen healthy male subjects (age 20-50 years, BMI 19-27 kg/m²) received 40 mg H 199/18 either as one 40 mg _____ tablet, two 20 mg _____ tablets or one 40 mg capsule for 3 days in an open, three-way crossover fashion separated by a washout period of at least 6 days. In each treatment period, blood samples were drawn for determination of H 199/18 before and at 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 8 hrs post-dose on day 3.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method _____ (LOQ = _____ nmol/L).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each formulation of H 199/18 using non-compartmental analysis: t_{max} , C_{max} , $t_{1/2}$, AUC_{0-t} and $AUC_{0-\infty}$.

Results

Table 1. Estimates of means of the primary PK parameters for H 199/18 after administration of 40 mg H 199/18 as one daily 40 mg \curvearrowright tablet, two daily 20 mg — tablets or one daily 40 mg capsule for 3 days

PK Parameter	40 mg \times 1 — Tablet	20 mg \times 2 — Tablet	40 mg \times 1 Capsule
t_{max}	2.00	1.82	2.10
C_{max}	2.39	2.11	2.02
AUC_{0-t}	4.50	4.09	4.10
$AUC_{0-\infty}$	4.58	4.17	4.18
$t_{1/2}$	0.94	0.92	0.93

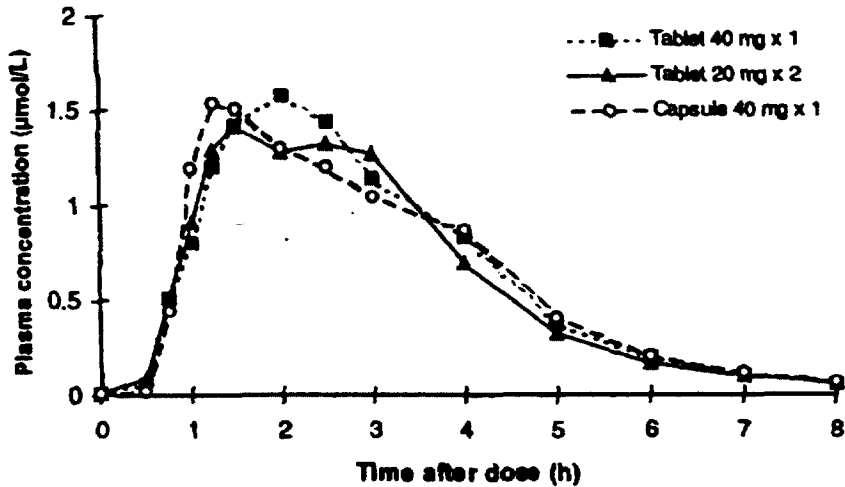


Figure 11:1 Mean plasma concentrations of H 199/18 following a single oral dose of different formulations of H 199/18 to healthy male subjects (n=18). Values below LOQ are set to half the LOQ value.

Reviewer's Comments

The data indicates that the 40 mg — tablet meets the bioequivalence criteria on AUC, but not on C_{max} , when compared to the 20 mg \curvearrowright tablet and to the 40 mg capsule. Hence, neither the two — tablet formulations nor the — tablet and capsule formulations are bioequivalent.

NDA: 21-153/ Study SH-QBE-0029

Study Date: Jan-Feb 1998

Type of Study: Relative Bioavailabilities of H 199/18 Capsule Formulations

Study SH-QBE-0029 is entitled,

“A RELATIVE BIOAVAILABILITY STUDY OF H 199/18 AFTER ADMINISTRATION OF TWO CAPSULE FORMULATIONS IN HEALTHY MALE SUBJECTS”.

Objectives

To determine the bioavailability of the capsule formulation of H 199/18 used in Phase III studies relative to that of the capsule formulation used in the Phase I/II studies after a single oral dose in healthy male subjects.

Primary Review Issue

How do two capsule formulations of H 199/18 compare with respect to their bioavailabilities?

Study Design

Eighteen healthy male subjects (age 20-50 years, BMI 19-27 kg/m²) received a single 40 mg H 199/18 dose of either Phase I/II capsule (batch # H 1222-01-01-02) or Phase III capsule (batch # H 1222-04-01-05) in an open, two-way crossover fashion separated by a washout period of at least 6 days. In each treatment period, blood samples were drawn for determination of H 199/18 before and at 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 8 hrs post-dose.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method _____ (LOQ = _____ nmol/L).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each formulation of H 199/18 using non-compartmental analysis: t_{max} , C_{max} , $t_{1/2}$, AUC_{0-t} and $AUC_{0-\infty}$.

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Results

Table 1. Estimates of the means of the primary PK parameters for H 199/18 after administration of a single 40 mg H 199/18 as either Phase I/II capsule or Phase III capsule

PK Parameter	40 mg × 1 Phase I/II Capsule	40 mg × 1 Phase III Capsule	Parameter Ratios (95% CI)
t_{max}	1.79	1.99	
C_{max}	2.55	2.34	0.92 (0.82-1.03)
AUC_{0-t}	4.05	3.78	0.93 (0.84-1.03)
$AUC_{0-\infty}$	4.11	3.84	0.93 (0.84-1.03)
$t_{1/2}$	0.84	0.86	

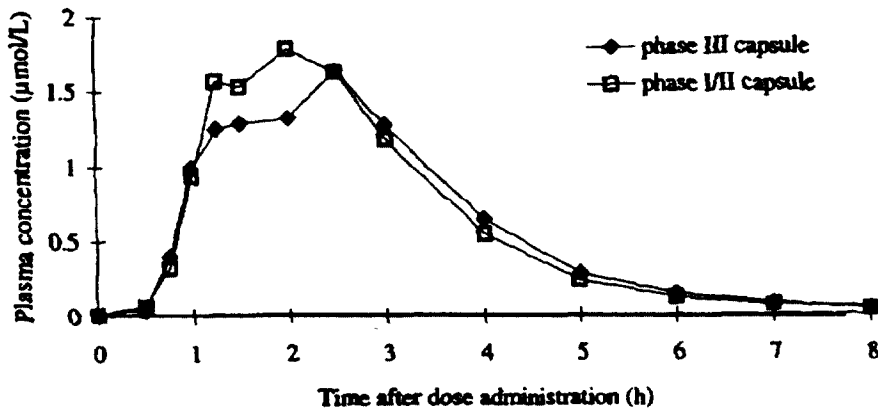


Figure 11:1 Mean plasma concentration of H 199/18 following a single oral dose of two different capsule formulations to healthy male subjects (n=18).

Reviewer's Comments

- The relative bioavailability of the Phase III capsule relative to the Phase I/II capsule is 93%. The two 40 mg capsule formulations of H 199/18 are deemed bioequivalent.

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NDA: 21-153/ Study DC-QBE-0002

Study Date: Jun-Oct 1998

Type of Study: Bioequivalence of ~~Tablet~~ Tablet and Phase III Capsule Formulations Under Fed Conditions

Study DC-QBE-0002 is entitled,

“A BIOEQUIVALENCE STUDY WITH 40 mg H 199/18 COMPARING A NEW TABLET FORMULATION WITH A CAPSULE FORMULATION IN HEALTHY SUBJECTS”.

Objectives

To determine whether a 40 mg ~~capsule~~ tablet formulation of H 199/18 is bioequivalent to the phase III capsule formulation under fed conditions during single and multiple dosing regimens.

Primary Review Issue

Is the ~~capsule~~ tablet bioequivalent to the Phase III capsule of H 199/18 when administered under fed conditions?

Study Design

Healthy male and female subjects (n = 76, age 20-50 years) received 40 mg H 199/18 once daily dose of either a ~~capsule~~ tablet (batch # H 1356-01-01-01) or a Phase III capsule (batch # H 1222-04-01-05) under fed conditions (after standard breakfast) for 5 days in an open, two-way crossover fashion separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of H 199/18 **before and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 14 and 16 hrs post-dose.**

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method ~~101~~ (LOQ = ~~0.5~~ nmol/L).

Pharmacokinetics

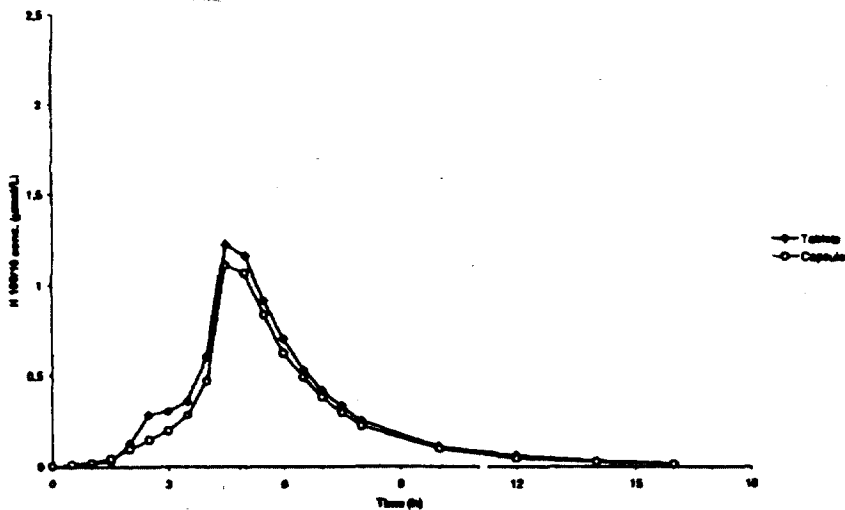
The following pharmacokinetic parameters were estimated for each formulation of H 199/18 using non-compartmental analysis: t_{max} , C_{max} , $t_{1/2}$, AUC_{0-t} and $AUC_{0-\infty}$.

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Results

Table 1. Estimates of the means of the primary PK parameters for H 199/18 after administration of 40 mg H 199/18 once daily dose as either Phase III capsule or tablet for 5 days

PK Parameter	Phase III Capsule	Tablet	Parameter Ratios (94% CI)
Day 1			
C_{max}	1.05	1.30	1.24 (1.09-1.42)
AUC_{0-t}	2.43	3.09	1.27 (1.13-1.43)
$AUC_{0-\infty}$	2.83	3.60	1.27 (1.15-1.41)
Day 5			
C_{max}	2.24	2.89	1.29 (1.18-1.42)
AUC_{0-t}	6.83	9.47	1.39 (1.29-1.49)
$AUC_{0-\infty}$	6.94	9.58	1.38 (1.28-1.48)



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Figure 11:1 Mean plasma concentrations versus time profile for H 199/18 following a single oral dose of 40 mg (day 1) administered as a tablet (n = 76) or as a capsule (n = 76). Values below the LOQ are set to LOQ/2.

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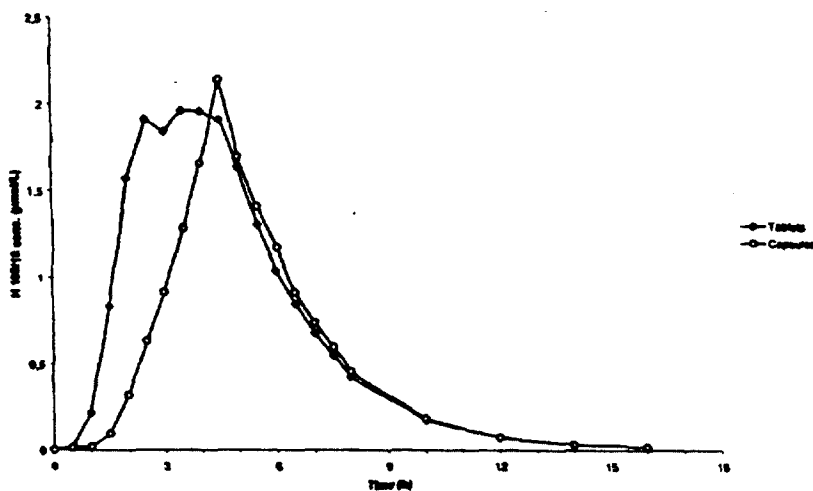


Figure 11:2 Mean plasma concentrations versus time profile for H 199/18 following repeated administration of 40 mg o.d. for five days (day 5) as a tablet (n = 76) or as a capsule (n = 76). values below the loq are set to loq/2.

Reviewer's Comments

- Based on the two-step bioequivalence approach employed by the sponsor, the 40 mg tablet and the Phase III capsule 40 mg formulation of H 199/18 deemed bioequivalent under fed conditions.

NDA: 21-153/ Protocol no. 227

Study Date: Mar-Jun 1999

Type of Study: Bioequivalence of Intact and Open Capsules

Protocol 227 is entitled,

“A RANDOMIZED, SINGLE-CENTER, OPEN LABEL, TWO-PERIOD CROSSOVER, PHARMACOKINETIC STUDY, TO EVALUATE THE BIOEQUIVALENCE OF A SINGLE 40 mg H 199/18 DOSE ADMINISTERED AS AN INTACT CAPSULE AND AS AN OPEN CAPSULE IN HEALTHY MALE AND FEMALE VOLUNTEERS”.

Objectives

To assess whether a single 40 mg dose of H 199/18 administered in applesauce is bioequivalent to the same dose administered as intact capsule in healthy subjects.

Primary Review Issue

Are the intact and open Phase III capsule formulations of H 199/18 bioequivalent, and hence interchangeable?

Study Design

Healthy male and female subjects (n = 41, age 18-45 years, BMI 19-27 kg/m²) received 40 mg H 199/18 single dose of either the an intact Phase III capsule or open Phase III capsule mixed with applesauce (batch # H 1222-04-01-05) in an open, two-way crossover fashion separated by a washout period of at least 7 days. In each treatment period, blood samples were drawn for determination of H 199/18 before and at 0.5, 0.75, 1, 1.25, 1.5, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 4.5, 5, 6, 7, 8, 10 and 12 hrs post-dose.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method _____ (LOQ = _____ ng/ml).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each treatment of H 199/18 using non-compartmental analysis: t_{max} , C_{max} , $t_{1/2}$, AUC_{0-t} and $AUC_{0-\infty}$.

Results

Table 1. Estimates of the means of the primary PK parameters for H 199/18 after administration of a single dose of 40 mg H 199/18 as either intact or open Phase III capsule

PK Parameter	Intact Capsule	Open Capsule	Parameter Ratios (94% CI)
C_{max} (ng/ml)	934	868	0.930 (0.859-1.006)
AUC_{0-t} (ng·hr/ml)	1692	1674	0.990 (0.945-1.037)
$AUC_{0-\infty}$ (ng·hr/ml)	1708	1689	0.989 (0.944-1.036)

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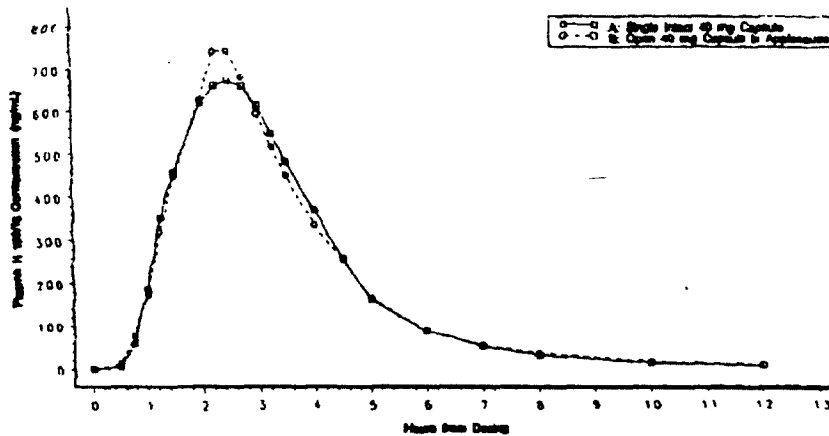


Fig. 1. Mean plasma concentration over time profiles after administration of a single 40 mg dose of H 199/18 as either an intact or open capsule

Reviewer's Comments

- Based on estimated geometric means and confidence intervals of C_{max} and $AUC_{0-\infty}$, the intact and open Phase III 40 mg capsule formulations of H 199/18 are considered to be bioequivalent.

NDA: 21-153/ Study SH-QBE-0033

Study Date: Apr-Jun 1998

Type of Study: Bioequivalence of Tablet and Capsule Formulations

Study SH-QBE-0033 is entitled,

“A BIOEQUIVALENCE STUDY WITH 20 mg H 199/189 COMPARING A NEW TABLET FORMULATION WITH A CAPSULE FORMULATION IN HEALTHY SUBJECTS”.

Objectives

To determine whether the phase III capsule formulation of H 199/18 and a ——— tablet formulation of 20 mg H 199/19 are bioequivalent following single and repeated dose administration.

Primary Review Issue

Are the ——— tablet and clinical trial capsule formulations of H 199/18 bioequivalent, and hence interchangeable?

Study Design

Healthy male and female subjects (n = 34, age 20-50 years, BMI 19-27 kg/m²) received 20 mg H 199/18 once daily dose of either the ——— tablet (batch # H 1370-01-01-01) or a Phase III capsule (batch # H 1189-04-01-04) for 5 days under fasting conditions in an open, two-way crossover fashion separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of H 199/18 before and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 7, 8, 10 and 12 hrs post-dose.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method ——— LOQ = ——— nmol/L).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each formulation of H 199/18 using non-compartmental analysis: t_{max}, C_{max}, t_{1/2}, AUC_{0-t} and AUC_{0-∞}.

Results

Table 1. Estimates of the means of the primary PK parameters for H 199/18 after administration of 20 mg H 199/18 once daily dose as either Phase III capsule or ——— tablet for 5 days

PK Parameter	Phase III Capsule	————— Tablet	Parameter Ratios (94% CI)
Day 1			
C _{max}	1.41	1.56	1.10 (0.95-1.28)
AUC _{0-t}	2.08	2.13	1.02 (0.93-1.12)
AUC _{0-∞}	2.12	2.17	1.02 (0.93-1.12)
Day 5			
C _{max}	2.41	2.47	1.02 (0.93-1.12)
AUC _{0-t}	4.67	4.70	1.01 (0.93-1.10)
AUC _{0-∞}	4.73	4.77	1.01 (0.93-1.10)

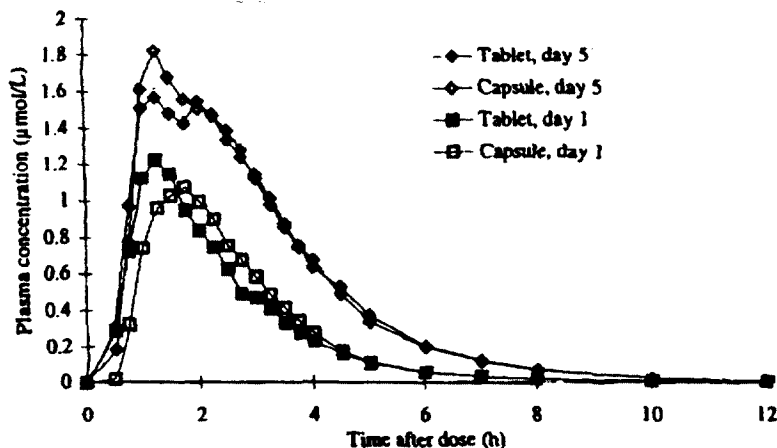


Figure 11.1: Mean plasma concentrations of H 199/18 following single (day 1) and multiple (day 5) oral doses of 20 mg H 199/18 given as a capsule or tablet to healthy subjects (n=34). Values below LOQ are set to half the LOQ value.

Reviewer's Comments

- Based on estimated geometric means and confidence intervals of C_{max} and $AUC_{0-\infty}$, the tablet 20 mg and the Phase III capsule 20 mg formulations of H 199/18 are deemed bioequivalent.

NDA: 21-153/ Study SH-QBE-0035

Study Date: Feb-May 1998

Type of Study: Bioequivalence of Tablet and Phase III Capsule Formulations Under Fasting Conditions

Study SH-QBE-0035 is entitled,

“A BIOEQUIVALENCE STUDY WITH 40 mg H 199/18 COMPARING A NEW TABLET FORMULATION WITH A CAPSULE FORMULATION IN HEALTHY SUBJECTS”.

Objectives

To determine whether a 40 mg tablet formulation of H 199/18 is bioequivalent to the phase III capsule formulation under fasting conditions during single and multiple dosing regimens.