## IN VITRO DRUG-DRUG INTERACTIONS USING HUMAN LIVER MICROSOMES

This study was designed to investigate the potential drug-drug interaction between memantine and a range of selected substrates (marker-substrate) routinely used to phenotype drug-metabolising enzyme activities in man. This study only looks at the inhibition potential of memantine on the CYP enzyme activities.

The activities measured in this study include

- methoxyresorufin O-dealkylation (marker of CYP1A2 activity),
- coumarin 7-hydroxylation (marker of CYP2A6 activity),
- tolbutamide 4-hydroxylation (marker of CYP2C9 activity),
- dextromethorphan O-demethylation (marker of CYP2D6 activity),
- 4-nitrophenol hydroxylation (marker of CYP2E1 activity),
- cortisol 6β-hydroxylation (marker of CYP3A activity),
- methimazole oxidation (marker of flavin containing mono oxygenase activity),
- phenanthrene 9, 10 hydrolysis (marker of epoxide hydroxylase activity),
- glucuronidation of 1-naphthol and testosterone, and
- sulphation of 1-naphthol.

Each of the marker substrate activities measured were expressed as a percentage of the respective control activity *(ie* rate of reaction in the absence of memantine).

Memantine (100 μM) was also incubated with human liver microsomes. Human liver microsomes were prepared from only one donor. Human liver microsomes used in this work were prepared and stored at -80°C. The viability of the microsomal preparation was evaluated prior to inclusion in this study. The concentrations of memantine used in this study were 0.1, 1.0 and 10 μM. Memantine was pre incubated with the human liver microsomes for 20 minutes before the addition of marker substrate.

Effect of memantine on marker-substrate activities:

Table I shows that marker-substrate activities measured in the presence of memantine were marginally higher than the respective control activities for methoxyresorufin O-dealkylation. coumarin 7-hydroxylation, tolbutamide 4-hydroxylation and cortisol 6β-hydroxylation.

Reaction mixtures set up to assess the effect of pre-incubating memantine with human liver microsomes (20 min), before the addition of a marker-substrate, gave marginally higher activities for methoxyresorufin O-dealkylation, coumarin 7-hydroxylation and 4-nitrophenol hydroxylation than their respective controls, indicating some degree of induction. With the exception of methimazole oxidation, the remaining Phase I reactions were either not affected by the addition of memantine (0.1-10 μM) or only marginally lower than the respective control activity. Reactions marginally affected by the addition

of memantine to the reaction mixtures were the mechanism-based reactions measuring tolbutamide 4-hydroxylation (CYP2C9), cortisol 6β-hydroxylation (CYP3A4) and phenanthrene 9, 10 oxide hydroxylation. These showed a low potential of inhibition of ≤ 18% except dextromethorphan O-demethylation (CYP2D6) (maximum inhibition of 22% of 1 μM memantine). All other reactions showed less than 11% inhibition.

The greatest inhibition of marker-substrate activity observed in this study was the oxidation of methimazole (21, 23, 41%) following a 20 minute pre-incubation of memantine (0.1, 1, 10 μM) with human liver microsomes. The oxidation of methimazole is used as a selective marker of flavin-containing mono-oxygenase activity (Ziegler's enzyme; Dixit *el Al,* Arch Biochem Biophys, 1984, 233, 50) and inhibition of this activity would therefore suggest an interaction between the two compounds for this enzyme.

Average in vivo steady state plasma concentration of memantine following administration of 20 mg daily dose were around 80 ng/mL (0.37 μM). This was well below the 10 μM memantine concentration that resulted in the inhibition of flavin containing monooxygenase. Based on these results, it is unlikely to expect inhibition of microsomal enzymes in vivo.

Table 2 shows that the glucuronidation of 1-naphthol and the sulphation of 1-naphthol were not affected by the addition of memantine to the reaction mixtures. There was some degree of reduction in the glucuronidation of testasterone.

TABLE 1

The Effect of Memantine on Phase I Reactions

| Memantine Concentration | % of Control Activity | | |
|---|---|---|---|
| | 0.1 μM | 1 μM | 10 μm |
| Methoxyresorufin O-dealkylation | 110 | 112 | 108 |
| Methoxyresorufin O-dealkylation (Mechanism-based) | 108 | 112 | 120 |
| Coumarin 7 hydroxylation | 104 | 108 | 128 |
| Coumarin 7-hydroxylation (Mechanism-based) | 108 | 116 | 122 |
| Tolbutamide hydroxylation | 103 | 111 | 106 |
| Tolbutamide hydroxylation (Mechanism-based) | 94 | 83 | 85 |
| Dextromethorphan O-demethylation | 89 | 109 | 98 |
| Dextromethorphan O-demethylation (Mechanism-based) | 99 | 78 | 87 |
| 4-Nitrophenol hydroxylation | 110 | 104 | 98 |
| 4 Nitrophenol hydroxylation (Mechanism-based) | 96 | 112 | 118 |
| Cortisol 6β hydroxylation | 92 | 106 | 113 |
| Cortisol 6β hydroxylation (Mechanism-based) | 94 | 82 | 90 |
| Methimazole oxidation | 98 | 92 | 95 |
| Methimazole oxidation (Mechanism-based) | 79 | 77 | 59 |
| Phenanthrene 9,10 oxide hydroxylation | 95 | 103 | 100 |
| Phenanthrene 9, 10 oxide hydroxylation (Mechanism-based) | 93 | 103 | 85 |

Reactions containing memantine are expressed as a % of the Control (no memantine)

Mechanism-based reactions: reactions incubated with memantine for 20 min prior to the addition of marker-substrate

TABLE 2

The Effect of Memantine on Phase II Reactions

| Memantine Concentration | % of Control Activity | | |
|---|---|---|---|
| | 0.1 μM | 1.0 μM | 10 μM |
| 1-Naphthol glucuronidation | 115 | 111 | 114 |
| Testosterone glucuronidation | 112 | 89 | 96 |
| 1-Naphthol sulphation | 100 | 93 | 93 |

Reactions containing memantine are expressed as a percentage of the Control (no memantine)

*Reviewer's Comments:*

- *The induction potential of memantine has not been evaluated*
- *Inhibition potential has been studied with just one donor which is not adequate and may not be representative of all isoenzymes from one individual.*

# EXTRINSIC FACTORS
# (DRUG-DRUG INTERACTIONS)

***Study: MRZ 90001-9702:*** ***Study of Pharmacokinetic Interaction Between Memantine and Hydrochlorothiazide/Triamterene Under Steady state Conditions***

***Objectives:***

To evaluate the rate and extent of absorption of memantine immediate release (IR) tablets and hydrochlorothiazide/triamterene (HCTZ/TA) immediate release tablets when given alone and in combination under steady state conditions. HCTZ/TA is a common drug combination administered for the treatment of edema, hypertension and congestive heart failure. Literature suggests that HCTZ accumulates after multiple dosing, hence a steady state study was chosen.

The clearance of memantine is largely renal and dependent on active tubular excretion. Due to its mainly renal excretion, an interaction with other drug substances with the same elimination mechanism may be likely. HCTZ is not metabolized and is excreted unchanged in the urine, whereas TA is mainly excreted in urine in the form of metabolites with only little unchanged TA.

The study design is as follows:

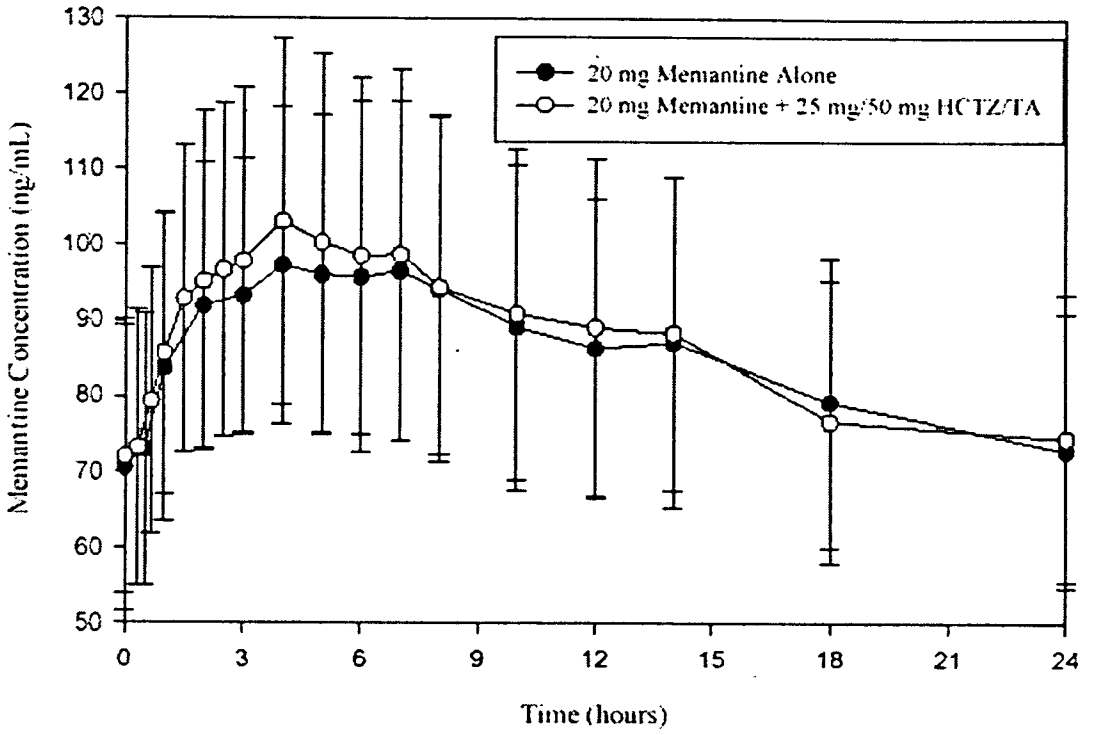
| | |
|---|---|
| Study Design | Open-label, randomized, 3-period repeated design, multiple dose study |
| Study Population | N=21 Healthy subjects enrolled, 20 completed<br>Age: 51-70 years<br>Gender: 9 males and 11 females<br>Weight: 75.7 kg, mean males 81.06 kg, females 71.31 kg<br>Race: Caucasians |
| Treatment Group | Each subject received the following treatment:<br>Period 1: 25 mg HCTZ + 50 mg TA, once daily for 4 days (Days 1-4)<br>Period 2: 5 mg memantine HCl, once daily for 3 days (Days 5-7), followed by 10 mg memantine HCl, once daily for 4 days (Days 8-11), followed by 20 mg memantine HCl, once daily for 14 days (Days 12-25)<br>Period 3: 20 mg memantine HCl and 25 mg HCTZ + 50 mg TA, once daily for 7 days (Days 26-32) |
| Dosage and Administration | 10 mg mematine HCl film coated tablet, Lot 61130, given as ½ tablet, 1 tablet or two tablets depending on the study days<br>25 mg Hydroclorothiazide (HCTZ)/50 mg Triamterene (TA), Lot 40802801<br>Tablets taken with 200 mL water.<br>Diet:<br>Fasted for 12 hours prior to dosing on blood sampling day 4, 25 and 32, meals given at 4 hours postdosing. On other days meals were served at 3, 6, and 12 hours post dose |

| | |
|---|---|
| | Volunteers abstained from alcohol for the duration of the study. Coffee, tea etc were also not permitted |
| Sampling: Blood | For memantine, hydrochlorothiazide, triamterene and the active metabolite hydroxytriamterene (OH-TA):<br>Blood samples for pharmacokinetic profiling were obtained on Day 4 (HCTZ/TA alone), on Day 25 (memantine alone) and on Day 32 (memantine and HCTZ/TA) according to the following blood schedule:<br>Day 4: 0 (pre-dose), 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 11, 14, 18, and 24 hours after dosing on Day 4.<br>Day 25: 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, and 24 hours after dosing on Day 25.<br>Day 32: 0 (pre-dose), 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, and 24 hours after dosing on Day 32.<br>Additional blood samples were obtained prior to dosing on Days 1, 2, 3, 23, 24, 30, and 31 for determination of trough plasma concentrations. |
| Urine | none |
| Feces | none |
| Analysis | for memantine samples<br>for HCTZ<br>TA and metabolites OH-TA<br><br>Lower Limits of Quantitation<br>Plasma<br>Memantine<br><br>HCTZ<br>for QC samples)<br><br>TA<br>for QC samples)<br><br>OH-TA<br>for QC samples)<br><br>Again memantine assay does not contain QC samples, but daily standard curves provided.<br>QC for other moieties provided and acceptable |
| PK Assessment | AUC0-t, Cmax, Cav, Cmin, PTF, Tmax |
| Safety Assessment | Adverse events, HR, RR, Clinical and lab exam, ECG, sodium, potassium, calcium |

***Pharmacokinetic Results:***

Memantine Plasma Concentrations:

The mean steady-state plasma concentration-time profiles of memantine following administration of memantine alone and in combination with HCTZ/TA are shown in the following Figure.




Mean plasma memantine concentrations were similar following multiple dose administration of memantine in combination with HCTZ/TA as compared to memantine alone.

The mean (SD) pharmacokinetic parameters of memantine in all subjects, male subjects and female subjects are summarized in the following Table.

**Table:**
**Pharmacokinetic Parameters (Mean ± SD) of Memantine Following Multiple Doses of 20 mg Memantine Alone and in Combination with 25 mg/50 mg Hydrochlorothiazide/Triamterene in Elderly Male and Female Subjects**

| *Parameter* | *20 mg Memantine Alone* | | | *20 mg Memantine + 25mg/50 mg HCTZ/TA* | | |
|---|---|---|---|---|---|---|
| | *All Subjects (n = 20)* | *Males (n = 9)* | *Females (n = 11)* | *All Subjects (n=20)* | *Males (n = 9)* | *Females (n = 11)* |
| $C_{max}$ (ng/mL) | 100.7 ± 21.3 | 96.6 ± 20.3 | 104.0 ± 22.5 | 106.2 ± 24.6 | 87.2 ± 23.2 | 113.5 ± 24.2 |
| $T_{max}$ (h) | 4.45 ± 2.57 | 4.23 ± 2.64 | 4.64 ± 2.62 | 3.78 ± 1.57 | 3.39 ± 1.58 | 4.10 ± 1.57 |
| $AUC_{0-24}$ (ng h/mL) | 2057 ± 479 | 1959 ± 433 | 2137 ± 520 | 2104 ± 496 | 1905 ± 402 | 2267 ± 523 |
| $C_{min}$ (ng/mL) | 69.5 ± 17.8 | 66.7 ± 16.0 | 71.8 ± 19.6 | 71.3 ± 17.6 | 65.4 ± 16.1 | 76.1 ± 18.0 |
| $C_{av}$ (ng/mL) | 85.7 ± 20.0 | 81.6 ± 18.0 | 89.1 ± 21.7 | 87.7 ± 20.7 | 79.4 ± 16.7 | 94.5 ± 21.8 |
| PTF (%) | 37.3 ± 5.7 | 37.1 ± 5.1 | 37.4 ± 6.5 | 40.2 ± 9.4 | 40.1 ± 7.0 | 40.4 ± 11.3 |

- Based on data from all subjects, mean Cmax, AUC0-24, Cmin, Cav, and PTF values were similar after the administration of memantine with HCTZ/TA compared to memantine alone.

Statistical evaluation of the pharmacokinetic interaction between memantine and HCTZ/TA was performed using an analysis of variance (ANOVA) model which included the effects of treatment and subject on log-transformed data for the AUC0-24, Cmax, and PTF parameters. The 90% confidence interval for the mean treatment ratios of Cmax and AUC0-24 were within the 80% - 125% range indicating that multiple dose administration of 25 mg/50 mg HCTZ/TA did not affect the bioavailability of memantine at steady state

**Table:**
**Statistical Comparisons of Memantine Pharmacokinetic Parameters Following Multiple Doses of 20 mg Memantine Alone and in Combination with 25 mg/50 mg Hydrochlorothiazide/Triamterene in Healthy Elderly Subjects**

| *Parameter* | *% Mean Ratio*[a] | *90% Confidence Interval* |
|---|---|---|
| $C_{max}$ | 105.2 | 100.3 – 110.3 |
| $AUC_{0-24}$ | 102.4 | 98.3 – 106.6 |
| PTF | 106.9 | 99.9 – 114.4 |

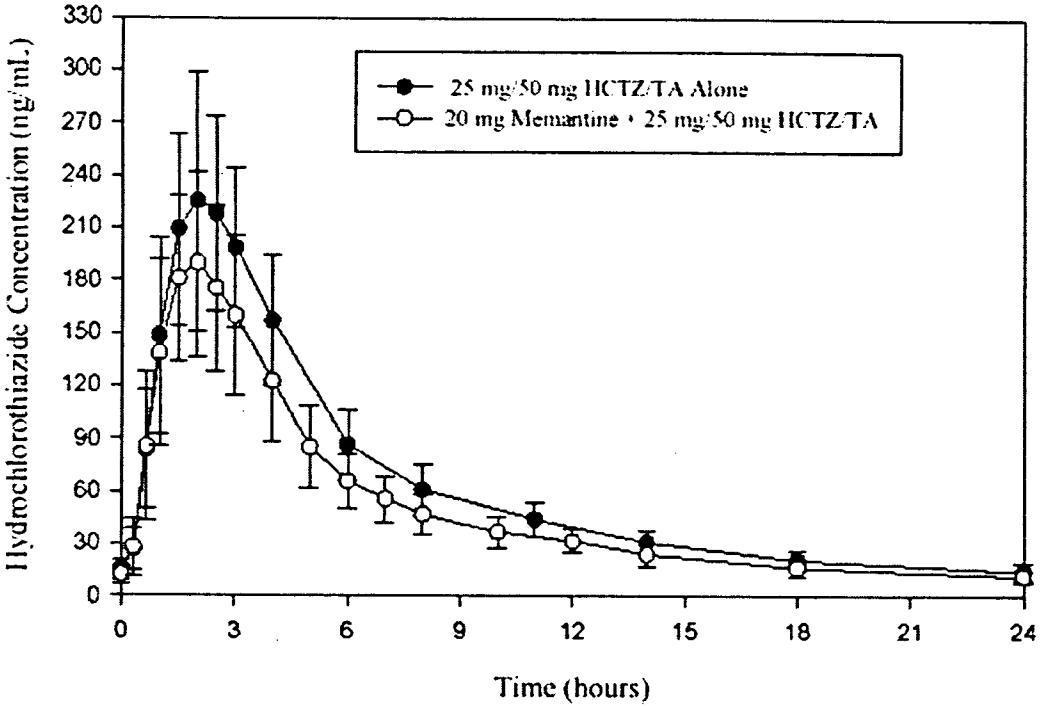
[a]Ratio of memantine in combination with HCTZ/TA to memantine alone.

- Gender Effect: The $C_{max}$, $AUC_{0-24}$, Cmin, Cav were higher in females whether memantine was given alone or in combination with HCTZ/TA. The differences were more pronounced when memantine was coadministered with HCTZ/TA. The peak trough fluctuation (PTF) appeared to be similar between male and female subjects when coadministered with HCTZ/TA

The effect of gender on the $AUC_{0-24}$ and $C_{max}$ parameters was evaluated using a second ANOVA model which included the effects of treatment, gender, subject within gender and treatment-by-gender interaction. Both the $AUC_{0-24}$ and $C_{max}$ parameters for memantine were significantly greater in female subjects ($p < 0.001$) when given with HCTZ/TA. Adjusting for weight did not change the conclusions.

HCTZ Plasma Concentrations:

The mean steady-state plasma concentration versus time profiles of hydrochlorothiazide following administration of 25 mg/50 mg hydrochlorothiazide/triamterene alone and in combination with 20 mg memantine are presented in the following Figure. Overall, lower mean plasma hydrochlorothiazide concentrations were observed when HCTZ/TA was co-administered with memantine as compared to HCTZ/TA alone.




The following Table summarizes the mean pharmacokinetic parameters of hydrochlorothiazide in all subjects, male subjects and female subjects.

**Table:**
**Pharmacokinetic Parameters (Mean ± SD) of Hydrochlorothiazide Following Multiple Doses of 25 mg/50 mg Hydrochlorothiazide/Triamterene Alone and in Combination with 20 mg Memantine in Elderly Male and Female Subjects**

| *Parameter* | *25mg/50 mg HCTZ/TA Alone* | | | *20 mg Memantine + 25mg/50 mg HCTZ/TA* | | |
|---|---|---|---|---|---|---|
| | *All Subjects (n = 20)* | *Males (n = 9)* | *Females (n = 11)* | *All Subjects (n=20)* | *Males (n = 9)* | *Females (n = 11)* |
| $C_{max}$ (ng/mL) | 246.0 ± 71.0 | 215.1 ± 48.7 | 271.4 ± 78.2 | 199.3 ± 52.5 | 179.6 ± 45.5 | 215.4 ± 54.3 |
| $T_{max}$ (h) | 2.18 ± 0.64 | 2.12 ± 0.83 | 2.23 ± 0.46 | 1.93 ± 0.52 | 2.12 ± 0.70 | 1.78 ± 0.26 |
| $AUC_{0-24}$ (ng h/mL) | 1523 ± 315 | 1417 ± 228 | 1609 ± 358 | 1220 ± 272 | 1107 ± 192 | 1311 ± 300 |
| $C_{min}$ (ng/mL) | 13.1 ± 4.5 | 12.6 ± 5.1 | 13.4 ± 4.1 | 11.4 ± 3.7 | 10.7 ± 2.7 | 11.9 ± 4.4 |
| $C_{av}$ (ng/mL) | 63.4 ± 13.1 | 59.0 ± 9.5 | 67.0 ± 14.9 | 50.8 ± 11.3 | 46.1 ± 8.0 | 54.6 ± 12.5 |
| PTF (%) | 365 ± 64 | 344 ± 63 | 383 ± 61 | 370 ± 55 | 367 ± 70 | 373 ± 43 |

- Lower mean HCTZ $AUC_{0-24}$, $C_{max}$, $C_{min}$, and $C_{av}$ values were observed when HCTZ/TA was co-administered with memantine. In the presence of memantine, mean $C_{max}$ and $AUC_{0-24}$ hydrochlorothiazide parameters were reduced by 19% and 20%, respectively. PTF values were similar.

Similar statistical analyses were performed for hydrochlorothiazide parameters as for memantine parameters. The 90% confidence interval for $AUC_{0-24}$ and $C_{max}$ was not within the range of 80% - 125 % indicating that multiple dose administration of 20 mg

memantine caused a significant decrease in the bioavailability of hydrochlorothiazide at steady-state.

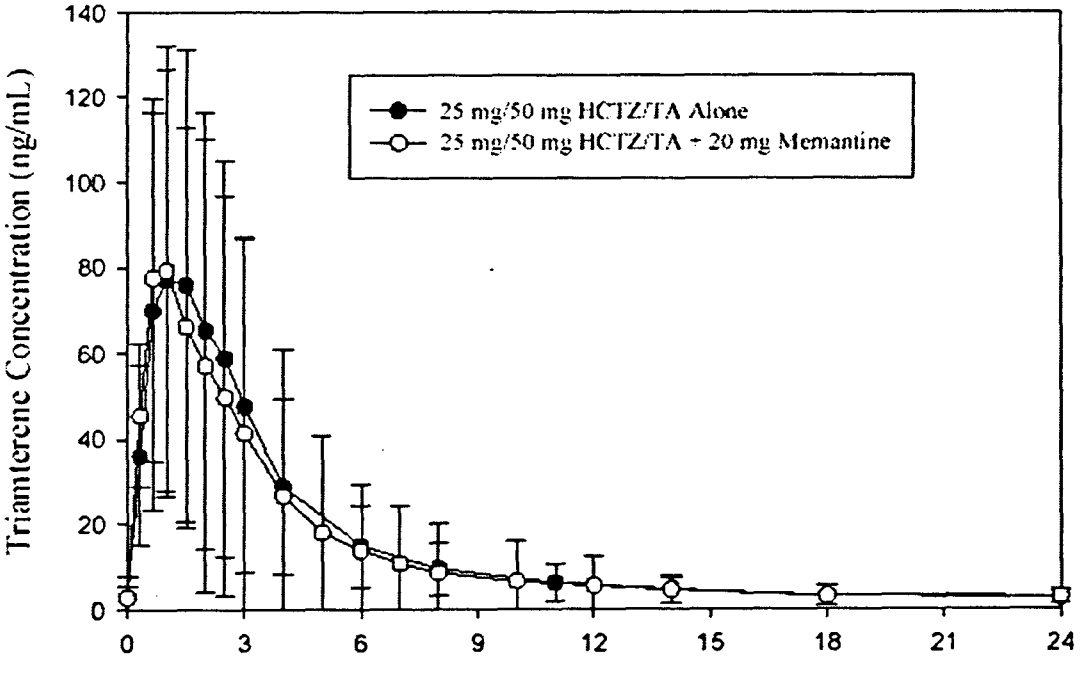
| **Table:**<br>**Statistical Comparisons of Hydrochlorothiazide Pharmacokinetic Parameters Following Multiple Doses of 25 mg/50 mg Hydrochlorothiazide/Triamterene Alone and in Combination with 20 mg Memantine in Healthy Elderly Subjects** | | |
|---|---|---|
| *Parameter* | % Mean Ratio[a] | 90% Confidence Interval |
| $C_{max}$ | 81.4 | 74.6 – 88.9 |
| $AUC_{0-24}$ | 79.9 | 74.8 – 85.2 |
| PTF | 101.6 | 96.4 – 107.2 |

[a]Ratio of HCTZ/TA in combination with memantine to HCTZ/TA alone

- Gender Effect: Female subjects had higher HCTZ $AUC_{0-24}$, $C_{max}$, $C_{min}$, $C_{av}$, and PTF values than male subjects regardless of treatment. Both the $AUC_{0-24}$ and $C_{max}$ parameters were significantly greater in female subjects (p = 0.002 for AUC0-24 and p = 0.001 for Cmax) regardless of treatment.

TA Plasma Concentrations:

The mean plasma concentrations of triamterene are presented in the following Figure. Similar mean plasma triamterene concentrations were observed when HCTZ/TA was administered alone and in combination with memantine.



The mean pharmacokinetic parameters of triamterene are summarized in the following Table.

**Table:**
**Pharmacokinetic Parameters (Mean ± SD) of Triamterene Following Multiple Doses of 25 mg/50 mg Hydrochlorothiazide/Triamterene Alone and in Combination with 20 mg Memantine in Elderly Male and Female Subjects**

| *Parameter* | *25mg/50 mg HCTZ/TA Alone* | | | *20 mg Memantine + 25mg/50 mg HCTZ/TA* | | |
|---|---|---|---|---|---|---|
| | *All Subjects (n = 20)* | *Males (n = 9)* | *Females (n = 11)* | *All Subjects (n=20)* | *Males (n = 9)* | *Females (n = 11)* |
| $C_{max}$ (ng/mL) | 88.4 ± 54.1 | 58.1 ± 43.0 | 113.1 ± 50.9 | 91.9 ± 52.6 | 58.6 ± 31.4 | 119.0 ± 51.5 |
| $T_{max}$ (h) | 1.28 ± 0.65 | 1.45 ± 0.83 | 1.15 ± 0.45 | 1.15 ± 0.88 | 1.61 ± 1.16 | 0.77 ± 0.22 |
| $AUC_{0-24}$ (ng h/mL) | 358 ± 215 | 280 ± 145 | 422 ± 247 | 334 ± 149 | 280 ± 107 | 379 ± 168 |
| $C_{min}$ (ng/mL) | 2.22 ± 1.43 | 2.22 ± 1.93 | 2.22 ± 0.95 | 2.15 ± 1.40 | 2.40 ± 1.96 | 1.95 ± 0.73 |
| $C_{av}$ (ng/mL) | 14.9 ± 9.0 | 11.7 ± 6.0 | 17.6 ± 10.3 | 13.9 ± 6.2 | 11.7 ± 4.4 | 15.8 ± 7.0 |
| PTF (%) | 588 ± 191 | 489 ± 258 | 669 ± 113 | 632 ± 203 | 494 ± 228 | 745 ± 77 |

- Similar mean pharmacokinetic parameters were observed when HCTZ/TA was co-administered with memantine. The results from the statistical evaluation of the pharmacokinetic interaction between triamterene and memantine showed that the 90% confidence intervals for the mean treatment ratio of Cmax and AUC0-24 parameters were within the range of 80% - 125%, indicating that multiple dose administration of 20 mg memantine did not affect the bioavailability of TA at steady state.

**Table:**
**Statistical Comparisons of Triamterene Pharmacokinetic Parameters Following Multiple Doses of 25 mg/50 mg Hydrochlorothiazide/Triamterene Alone and in Combination with 20 mg Memantine in Healthy Elderly Subjects**

| *Parameter* | *% Mean Ratio*[a] | *90% Confidence Interval* |
|---|---|---|
| $C_{max}$ | 107.2 | 92.9 – 123.7 |
| $AUC_{0-24}$ | 97.9 | 86.9 – 110.2 |
| PTF | 109.5 | 101.0 – 118.7 |

[a]Ratio of HCTZ/TA in combination with memantine to HCTZ/TA alone

- Gender Effect: Female subjects had higher Cmax, AUC0-24, Cav, and PTF values than male subjects regardless of treatment. Mean Cmax and AUC0-24 values were about 2 and 1.5 times greater in female subjects than in male subjects, respectively. Both the AUC0-24 and Cmax parameters were significantly greater in female subjects ($p<0.001$) regardless of treatment.

OH-TA Plasma Concentrations:

Similar mean plasma hydroxytriamterene concentrations were observed when HCTZ/TA was administered alone and in combination with memantine.

The pharmacokinetic parameters of hydroxytriamterene are summarized in the following Table.

**Table**
**Hydroxytriamterene Pharmacokinetic Parameters (Mean ± SD) Following Multiple Doses of 25 mg/50 mg Hydrochlorothiazide/Triamterene Alone and in Combination with 20 mg Memantine in Elderly Male and Female Subjects**

| *Parameter* | *25mg/50 mg HCTZ/TA Alone* | | | *20 mg Memantine + 25mg/50 mg HCTZ/TA* | | |
|---|---|---|---|---|---|---|
| | *All Subjects (n = 20)* | *Males (n = 9)* | *Females (n = 11)* | *All Subjects (n=20)* | *Males (n = 9)* | *Females (n = 11)* |
| $C_{max}$ (ng/mL) | 788 ± 282 | 629 ± 316 | 918 ± 172 | 855 ± 336 | 680 ± 297 | 999 ± 306 |
| $T_{max}$ (h) | 1.48 ± 0.67 | 1.74 ± 0.80 | 1.26 ± 0.47 | 1.43 ± 1.01 | 2.00 ± 1.30 | 0.96 ± 0.24 |
| $AUC_{0-24}$ (ng h/mL) | 3400 ± 680 | 3103 ± 628 | 3643 ± 646 | 3512 ± 863 | 3373 ± 590 | 3626 ± 1052 |
| $C_{min}$ (ng/mL) | 21.7 ± 9.3 | 20.4 ± 8.2 | 22.8 ± 10.4 | 24.2 ± 12.3 | 25.7 ± 16.3 | 22.9 ± 8.5 |
| $C_{av}$ (ng/mL) | 141.7 ± 28.3 | 129.3 ± 26.2 | 151.8 ± 26.9 | 146.3 ± 36.0 | 140.5 ± 24.6 | 151.1 ± 43.8 |
| PTF (%) | 560 ± 184 | 469 ± 228 | 598 ± 119 | 566 ± 169 | 465 ± 196 | 649 ± 81 |

- Similar mean pharmacokinetic parameters were observed when HCTZ/TA was administered alone and in combination with memantine.

The results from the statistical evaluation of the pharmacokinetic interaction between hydroxytriamterene and memantine showed that the 90% confidence intervals for the mean treatment ratio of Cmax and AUC0-24 parameters were within the range of 80% - 125%, indicating that multiple dose administration of 20 mg memantine did not affect the bioavailability of hydroxytriamterene at steady-state.

**Table:**
**Statistical Comparisons of Hydroxytriamterene Pharmacokinetic Parameters Following Multiple Doses of 25 mg/50 mg Hydrochlorothiazide/Triamterene Alone and in Combination with 20 mg Memantine in Healthy Elderly Subjects**

| *Parameter* | *% Mean Ratio*[a] | *90% Confidence Interval* |
|---|---|---|
| $C_{max}$ | 109.6 | 98.4 – 122.1 |
| $AUC_{0-24}$ | 102.4 | 92.3 – 113.6 |
| PTF | 106.7 | 99.6 – 114.2 |

[a]Ratio of HCTZ/TA in combination with memantine to HCTZ/TA alone

- Gender Effect: Female subjects had higher Cmax, AUC0-24, Cav, and PTF values than male subjects regardless of treatment. Cmax was significantly greater in females ($p<0.0001$) regardless of the treatment. AUC0-24 was not different regardless of the treatment.

Safety: Coadministration of both study drugs did not lead to any significant increase in AEs. There were no relevant effects on RR, HR or serum electrolytes in this period.

*Reviewer's Comment:*

*Only standard curve data provided. There is one standard curve per subject. No QC data available. The sponsor mentions in the response regarding clarification of assay*

*procedures that the tight standard curves reflect the accuracy and precision for the QC data as well. This study can be accepted due to previously mentioned reasons.*

**Conclusions:**

- Following multiple daily doses of 20 mg memantine and 25 mg/50 mg hydrochlorothiazide/triamterene, there were no statistically significant changes in the bioavailability of memantine. On the other hand, memantine caused a 20% reduction in the bioavailability of hydrochlorothiazide. Memantine did not appear to affect the bioavailability of triamterene or the degree of its conversion to the hydroxy metabolite. With respect to therapeutic consequences, a slightly reduced diuretic effect is possible when memantine is coadministered with HCT. Individual dose adjustment may be necessary.
- Greater bioavailability of memantine, hydrochlorothiazide, triamterene, and hydroxytriamterene (except for AUC0-24 of hydroxytriamterene) was observed in female versus male subjects. The most pronounced differences in Cmax and AUC values between female and male subjects were observed for triamterene. Adjusting for weight differences did not change this conclusion.

***Study: MEM-PK-07: A Study of the Pharmacokinetic Interaction of Memantine and Aricept in Healthy Young Subjects***

***Objectives:***

(a) To determine if there is an in vivo pharmacokinetic interaction between memantine and donepezil and
(b) To evaluate whether memantine affects the ability of donepezil to inhibit acetylcholinesterase activity.

Donepezil HCl (Aricept) is a piperidine based, specific inhibitor of acetylcholine esterase (AchE) that is currently approved for the treatment of mild to moderate Alzheimer's disease. During treatment with either memantine or donepezil, the other drug may be added as an adjunct therapy. In vitro studies have shown that memantine does not attenuate the inhibition of AchE produced by donepezil. This study is conducted to determine whether there is an in vivo pharmacokinetic interaction between memantine and donepezil.

The study design is as follows:

| | |
|---|---|
| Study Design | open label, single sequence, multiple dose study |
| Study Population | N=24 subjects , 19 completed , 5 subjects discontinued participation due to protocol violation, withdrawing consent, lost to follow up and adverse events during donepezil alone treatment<br>Age: 18-35 years, mean age 27.6 years<br>Gender: 16 males and 8 females<br>Weight: 50-88 kg , mean 73.6 kg<br>Race: NA |
| Treatment Group | None. All subjects got the same treatment |
| Dosage and Administration | Day 1: 1x10 mg memantine tablet<br>Followed by a 14 day washout<br>Day 15-21: 1x5 mg Aricept (donepezil) tablet once daily for 7 days<br>Day 22-43: 2x5 mg Aricept (donepezil) tablet once daily for 22 days<br>Day 43: 1x10 mg memantine tablet with the last dose of donepezil<br><br>10 mg memantine tablet lot no: 5007<br>5 mg Aricept tablet lot no 000808<br><br>Diet:<br>Assigned dosing of memantine under fasting conditions administered with 240 ml water on Days 1, 42 and 43. Received meals at 1200, 1700 and 2100 hours on these days.<br>Standardized meals at other times.<br>No caffeine, alcohol and grapefruit during the study |
| Sampling: Blood | For memantine :<br>On Day 1 : At 0.0-hour (pre-dose), 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120,144, 168, and 192 hours post-dose. |

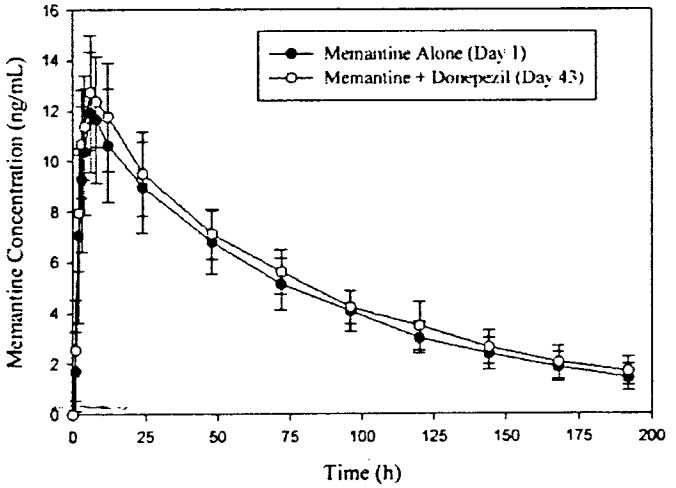
| | |
|---|---|
| | On Day 43: At 0.0-hr (pre-dose), 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, and 192 hours post-dose.<br><br>For donepezil :<br>On Days 15, 40, and 41 and Day 42 :At 0.0 hr (pre-dose) at 0.0-hr (pre-dose), 1,2, 3, 4, 6, 8, and 12 hours post-dose.<br>On Day 43: At 0.0-hr (pre-dose), 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose.<br><br>For AChE activity in RBCs:<br>On Day 15: (0.0-hour),<br>On Day 42: (0.0, 1, 2, 3, 4, 6, 8, and 12 hours)<br>On Day 43: (0.0, 1, 2, 3, 4, 6, 8, 12, and 24 hours |
| Urine | none |
| Feces | none |
| Analysis | — for memantine and donepezil samples<br><br>Lower Limits of Quantitation<br>Plasma<br>Memantine /<br>Donepezil /<br><br>Memantine:<br>Linear Range /<br>Inter and Intraday Precision —<br>Inter and Intraday Accuracy —<br>—<br><br>Quality control concentrations ng/ml<br>Stability: Human plasma for 24 hours at RT<br><br>Specificity: No interference<br>Recovery: —<br>Assay complete and acceptable<br><br>Donepezil:<br>Linear Range /<br>Inter and Intraday Precision /<br>Inter and Intraday Accuracy /<br>Quality control concentrations — ng/ml<br><br>Assay acceptable<br><br>AchE:<br>Radioenzyme assay<br>Interday Precision /<br>Intraday Precsion /<br>Quality control concentrations — ng/g |

| | |
|---|---|
| | Stability: /<br><br>Specificity: No interference<br>Recovery: — |
| PK Assessment | AUC, Cmax, Tmax, CL/F, VZ/F |
| PD Assessment | Amin, Amax, AUCA, % Inhibition, Imax, AUCI<br><br>% Activity: (Activity postdose/Activity predose)x 100<br><br>Amax is the maximum activity and Amin is the minimum activity expressed as a % baseline observed during the 0-24 hour interval on Days 42 and 43.<br><br>AUCA is the area under the %AchE activity versus time curve<br><br>% Inhibition = [(Activity predose-Activity postdose)/(Activity predose)] x 100 = 100 -% activity.<br><br>Imax is the maximum inhibition observed during the 0-24 hour interval on Days 42 and 43.<br><br>AUCI is the area under the % inhibition versus time curve |
| Safety Assessment | Blood pressure, pulse rate, ECG, Laboratory tests, hematology, blood chemistry |

***Pharmacokinetic Results:***

Effect of Donepezil on memantine pharmacokinetics:

The mean plasma concentrations of memantine when administered alone and in combination with donepezil are presented in the following Figure.



The mean (± SD) pharmacokinetic parameters of memantine when administered alone (Day 1) and with memantine (Day 43) and statistical comparisons of pharmacokinetic parameters (Cmax and AUC) on Day 43 (memantine administered with donepezil) versus Day 1 (memantine without donepezil) are given in the following Table:

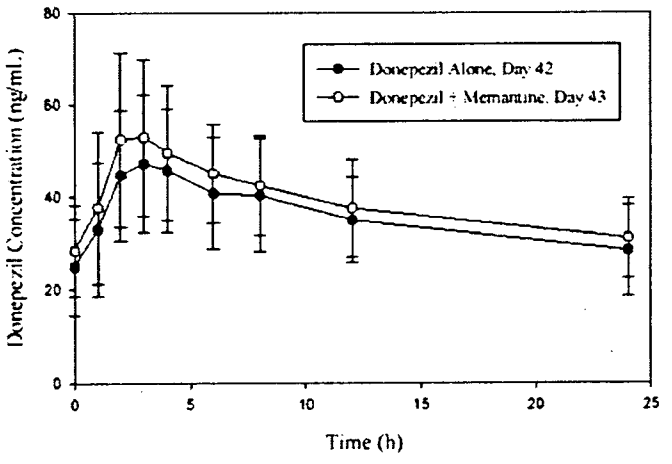
**Table: Pharmacokinetic Parameters of Memantine (Mean ± SD) Following Administration of 10 mg Memantine With or Without Donepezil**

| *Parameter* | *Without Donepezil (n = 19)* | *With Donepezil (n = 19)* | *Least Square Means Ratio* | *90% Confidence Interval* |
|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 12.8 ± 2.4 | 13.0 ± 2.0 | 101.0 | 98.6 -105.4 |
| $T_{max}$ (h) | 6.5 ± 2.1 | 6.5 ± 1.3 | - | - |
| $AUC_{0-t}$ (ng h/mL) | 958.4 ± 147.2 | 1002.7 ± 143.4 | 104.8 | 101.6 – 108.1 |
| $AUC_{0-\infty}$ (ng h/mL) | 1124.5 ± 211.3 | 1188.2 ± 222.6 | 105.7 | 102.0 – 109.7 |
| T½ (h) | 70.9 ± 24.1 | 72.3 ± 16.3 | - | - |
| CL/F (mL/min) | 127.3 ± 23.8 | 120.2 ± 21.2 | - | - |
| Vz/F (L) | 759.8 ± 202.2 | 735.0 ± 128.3 | - | - |
| MRT (h) | 98.9 ± 29.8 | 101.2 ± 19.5 | - | - |

- The 90% confidence intervals for the comparison of the log-transformed Cmax, AUC0-t, and AUC0- ∞ were within the range of 80-125% indicating that multiple daily dosing of 10 mg donepezil did not significantly alter the rate or extent of absorption of a single 10 mg memantine dose.

Effect of memantine on Donepezil Pharmacokinetics:

The mean plasma concentrations of donepezil when administered alone and in combination with memantine are presented in the following Figure.



The mean (± SD) pharmacokinetic parameters of donepezil when administered alone (Day 1) and with donepezil (Day 43) and statistical comparisons of pharmacokinetic parameters (Cmax and AUC) on Day 43 (donepezil administered with memantine) versus Day 42 (donepezil without memantine ) are tabulated in the following Table.

Attainment of steady state was evaluated by linear regression analysis following multiple dose administration of donepezil concentrations on Days 40, 41 and 42. Based on the p-value for the slope of the regression line, steady state was attained in a total of 15 subjects ($p>0.05$) but not in 4 subjects who completed the study ($p<0.05$).

**Table:**
**Pharmacokinetic Parameters of Donepezil (Mean ± SD) Following Multiple Dose Administration of 10 mg Donepezil Once Daily With or Without Memantine**

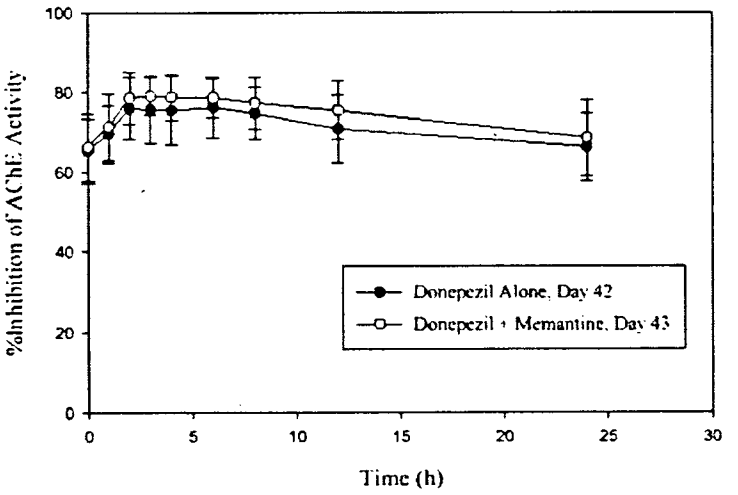
| *Parameter* | *Without Memantine (n = 19)* | *With Memantine (n = 19)* | *Least Square Means Ratio* | *90% Confidence Interval* |
|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 49.1 ± 14.5 | 55.4 ± 18.0 | 114.8 (all subjects)<br>111.5 (excl. 4) | 104.2-126.5<br>99.7 - 124.8 |
| $T_{max}$ (h) | 3.4 ± 1.5 | 3.3 ± 1.7 | | - |
| $AUC_{0-24}$ (ng h/mL) | 857.6 ± 246.5 | 934.4 ± 249.5 | 111 (all subjects)<br>108.0 (excl. 4) | 101.1-117.3<br>101.8 - 116.6 |
| CL/F (mL/min) | 215.9 ± 176.0 | 182.6 ± 91.8 | | - |

The 90% confidence interval for the log-transformed AUC0-24 was within the range of 80-125% indicating that single dose administration of 10 mg memantine did not alter the extent of absorption of multiple dose donepezil. The 90% confidence interval for the log-transformed Cmax was slightly outside the 80 – 125% range (104.2 - 126.5%).

After omitting from the statistical comparison of donepezil pharmacokinetic parameters data from the 4 subjects (Subjects 1, 5, 6, and 17) who did not reach steady-state ($p < 0.05$), the 90% confidence intervals for the comparison of the log-transformed Cmax and AUC0-24 were within the range of 80 – 125%.

AchE Measurements:

The mean percent inhibition of RBC AChE activity measurements are presented in the following Figure.




The mean (± SD) pharmacodynamic parameters for AchE and statistical comparisons of parameters on Day 42 (donepezil with memantine) and Day 42 (donepezil without memantine) are presented in the following Table.

**Table:**
**AChE Pharmacokinetic Parameters of Donepezil (Mean ± SD) Following Multiple Dose Administration of 10 mg Donepezil Once Daily With or Without Memantine**

| *Parameter* | *Without Memantine (n = 19)* | *With Memantine (n = 19)* | *Least Squares Means Ratio* | *90% Confidence Interval* |
|---|---|---|---|---|
| $I_{max}$ (% baseline) | 77.8 ± 7.3 | 81.1 ± 5.7 | 104.5 | 101.8 – 107.1 |
| $^{AUC}I$ (% baseline h) | 1708.1 ± 191.0 | 1748.8 ± 168.7 | 104.8 | 102.7 – 106.9 |
| Amin (% baseline) | 22.2 ±7.3 | 18.9 ± 5.7 | | |
| Amax (% baseline) | 35.7 ± 8.56 | 34.6 ± 8.96 | | |
| AUCA (% baseline h) | 692 ± 191 | 615 ± 168.7 | | |
| Imin (% baseline) | 64.3 8.5 | 65.4 ± 8.9 | | |

The 90% confidence intervals for the log-transformed Imax and AUCI were within the range of 80-125% indicating that inhibition of RBC AChE activity was not significantly altered by the coadministration of donepezil and memantine as compared to the administration of donepezil alone.

Adverse Events:

A total of 111 treatment emergent adverse events occurred, 98 of these were in subjects receiving donepezil alone, 3 occurred following memantine alone, and 10 occurred with coadministration. There were no serious adverse events. Common adverse events were headache, nausea, fatigue, weakness, dizziness, vomiting and lightheadedness. No

clinically significant findings were observed in laboratory results, ECG interval or heart rate and vital signs.

***Conclusions:***

- Single dose memantine did not affect the pharmacokinetics of steady-state donepezil.
- Multiple dose donepezil did not affect the pharmacokinetics of single dose memantine.
- Inhibition of RBC AchE by donepezil was not affected by coadministration of memantine.



APPEARS THIS WAY
ON ORIGINAL

## INTRINSIC FACTORS
## (SPECIAL POPULATIONS)

***Study: PAZ 3049:*** *Single Oral Application (20 mg) in 12 Geriatric Volunteers with Reduced Renal Functions; Determination of Plasma Levels, Total Clearance and Terminal Half-Lives. Additionally, Comparison of Fasting and Non-fasting Pharmacokinetics at Normal Renal Function in 6 Volunteers*

***Objectives:***

- To determine the plasma levels, total clearance and terminal half-life of memantine in elderly subjects with impaired renal function as compared to older subjects with normal renal function.
- To compare the pharmacokinetics of memantine under fasting and fed conditions in the group of subjects with normal renal function.

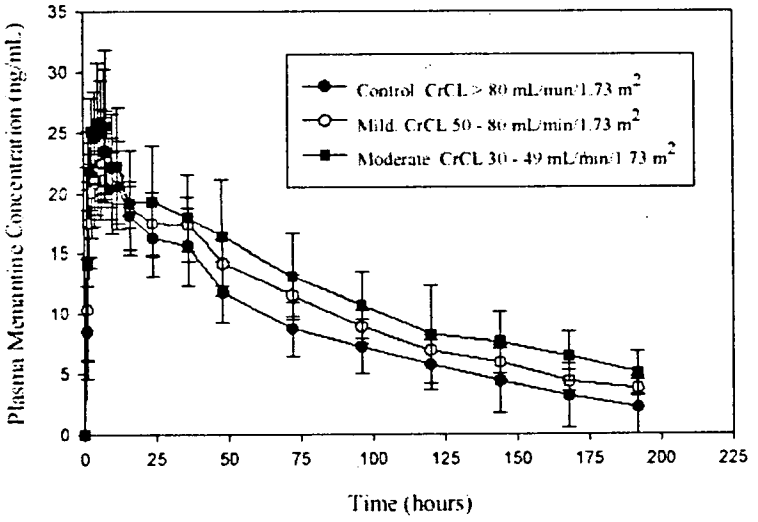
The study design is as follows:

| | |
|---|---|
| Study Design | Open-label, randomized, 2-period design, single dose study |
| Study Population | N=18 subjects<br>Age: 45-77 years<br>Gender: 8 males and 10 females<br>Weight: kg<br>Race: Caucasians |
| Treatment Group | Period 1: Subjects assigned to the following group based on CrCL values:<br>Control Group: CrCL greater than 80 mL/min/1.73 $m^2$ (n = 6)<br>Mild renal impairment: CrCL in the range 50 - 80 mL/min/1.73 $m^2$ (n = 9)<br>Moderate renal impairment: CrCL in the range 30 - 49 mL/min/1.73 $m^2$ (n = 3)<br>Period 2: 6 subjects with normal renal function received an additional 20 mg memantine dose under fed conditions following a 2 week washout phase |
| Dosage and Administration | All subjects received a single dose of 20 mg (2x10 mg) memantine under fasting conditions |
| Sampling: Blood | Over a 192-hour period at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 12, 36, 48, 72, 96, 120, 144, 168, and 192 hours post-dose. |
| Urine | At predose, 0-12, 12-24, 24-36 and 36-48 hours post-dose |
| Feces | none |
| Analysis | for memantine samples<br>Lower Limits of Quantitation<br>Plasma Urine<br>Memantine<br>Plasma: of calibration concentrations<br>Urine: calibration concentrations |

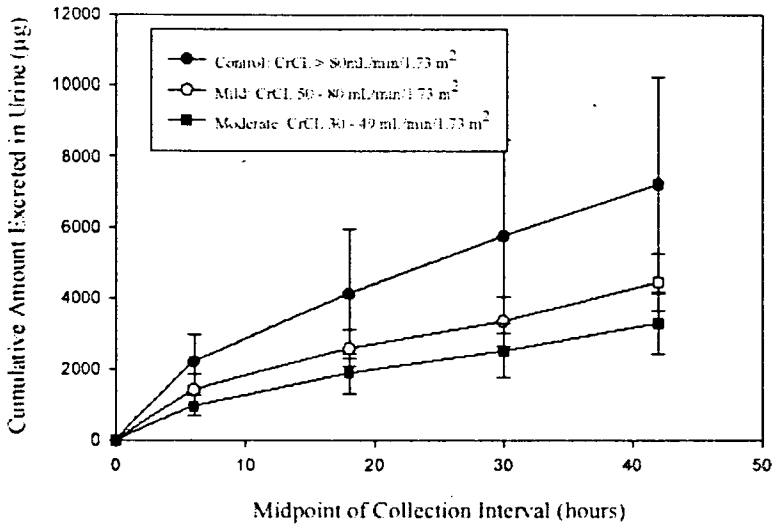
| | |
|---|---|
| | None of the validation parameters are provided. A new limit of quantitation which is lower than the validated range, assay validation not acceptable |
| PK Assessment | AUC, Cmax, Tmax, t1/2, CLr, CLtot, Ae0-48 |
| Safety Assessment | |

***Pharmacokinetic Results:***

The mean plasma memantine concentration profiles following a single oral dose of 20 mg memantine under fasting conditions in subjects with normal renal function, mild or moderate renal impairment are shown in the following Figure. It can be observed that the lowest mean plasma concentrations were observed in subjects with normal renal function and the highest mean values in subjects with moderate renal impairment.




The urinary excretion of unchanged memantine over a period of 48 hours post-dose is depicted in the following Figure. Urinary excretion was the highest in the subjects with normal renal function and lowest in the subjects with moderate renal impairment.




The pharmacokinetic parameters of memantine in plasma and urine are given in the following Table:

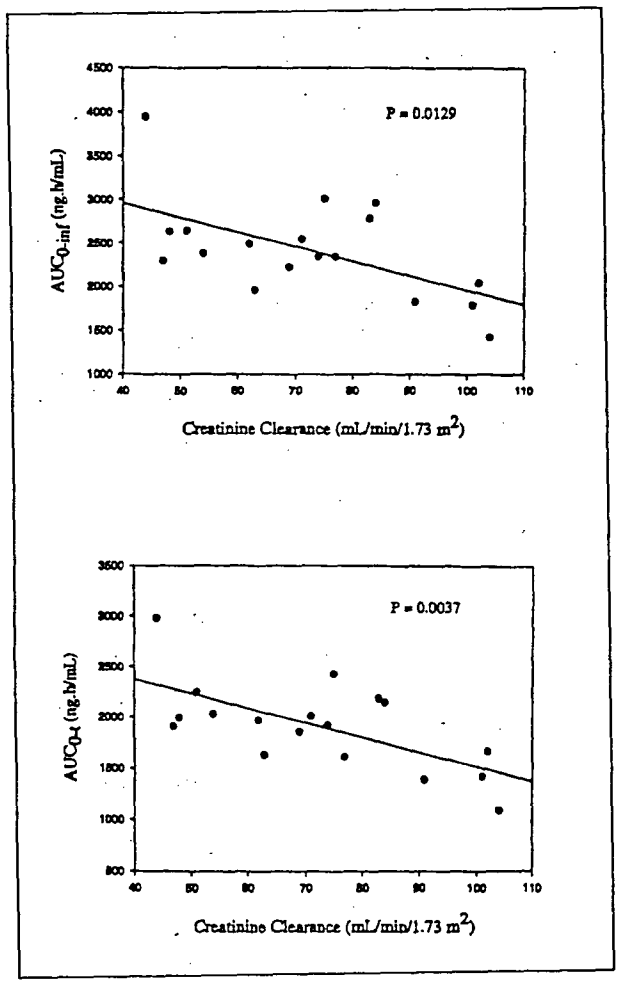
**Table:**
**Pharmacokinetic Parameters (Mean ± SD) of Memantine Following a Single 20 mg Oral Dose in Geriatric Subjects with Various Degrees of Renal Impairment**

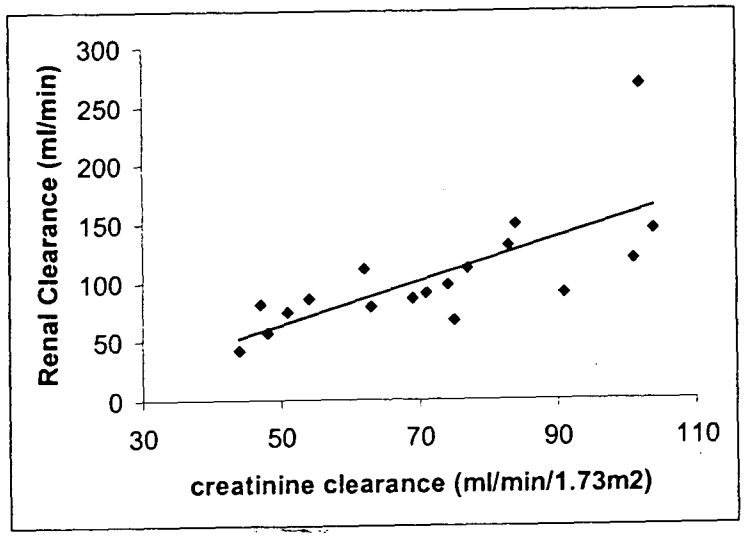
| *Parameter* | *Control (n = 6)* | *Mild (n = 9)* | *Moderate (n =3)* |
|---|---|---|---|
| CrCL (mL/min/1.73m$^2$) | 94.17 ± 9.41 | 66.22 ± 9.31 | 46.33 ± 2.08 |
| $t_{1/2}$ (h) | 84.58 ± 12.51 | 85.37 ± 25.38 | 89.79 ± 12.72 |
| $CL_{tot}$ (mL/min) | 136.8 ± 37.6 | 113.6 ± 13.5 | 97.3 ± 25.6[a] |
| $CL_r$ (mL/min) | 150.4 ± 61.5 | 89.3 ± 15.2 | 60.3 ± 19.9 |
| $Ae_{0-48}$ (µg) | 7217 ± 3017 | 4562 ± 741 | 3286 ± 857 |
| $AUC_{0-t}$ (ng h/mL) | 1645 ± 437 | 1961 ± 259 | 2293 ± 599 |
| $AUC_{0-\infty}$ (ng h/mL) | 2134 ± 608 | 2434 ± 292 | 2961 ± 875 |
| $C_{max}$ (ng/mL) | 23.12 ± 4.21 | 23.42 ± 2.36 | 26.91 ± 4.70 |
| $T_{max}$ (h) | 6.7 ± 2.0 | 7.6 ± 2.0 | 5.0 ± 2.6 |
| $V_d$ (L) | 968 ± 132 | 840 ± 274 | 743 ± 153[a] |

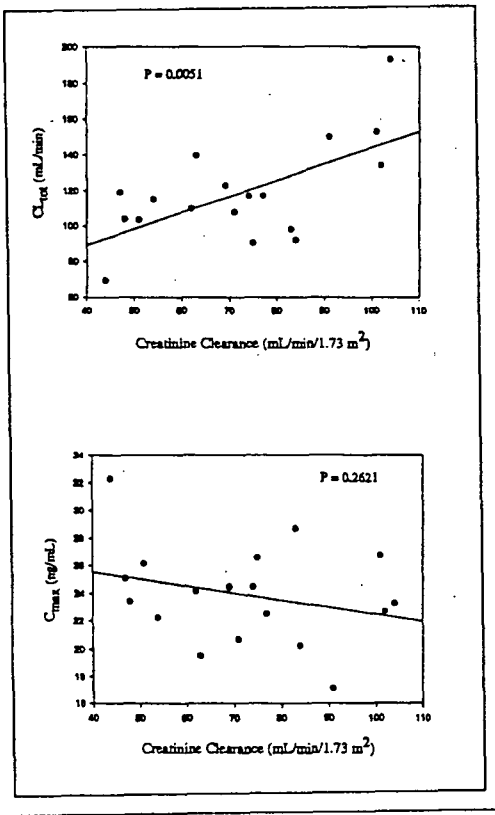
[a] Based on memantine free-base dose

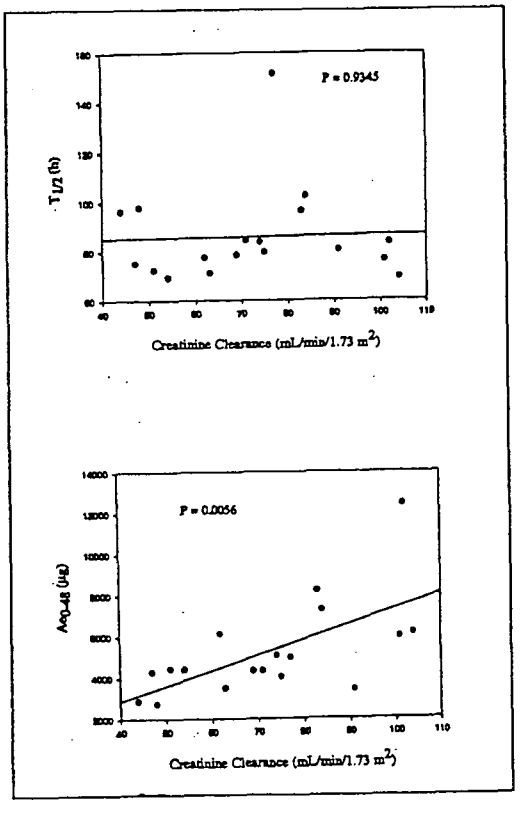
- Total clearance was reduced by 17% and 33% in mild and moderate renal impairment, respectively.
- Subjects with mild and moderate renal impairment had a mean increase in AUC0-∞ values by 14% and 39% relative to the subjects with normal renal function.
- Similar mean T1/2 values were obtained in subjects with normal renal function and mild renal impairment.

Linear regression of memantine pharmacokinetic parameters was performed as a function of creatinine clearance. Significant relationships with respect to creatinine clearance were observed for AUC0-t and AUC0-∞ which increased with reduced creatinine clearance (p = 0.0119 and 0.0037, respectively) and for CLtot, CLr and Ae0-48 which decreased with decreasing creatinine clearance (p = 0.0047 and 0.0056, respectively). No significant relationships were observed for T1/2 and Cmax versus CrCL.


P = 0.0129
$AUC_{0-inf}$ (ng.h/mL)
Creatinine Clearance (mL/min/1.73 $m^2$)
P = 0.0037
$AUC_{0-t}$ (ng.h/mL)
Creatinine Clearance (mL/min/1.73 $m^2$)


Renal Clearance (ml/min)
300
250
200
150
100
50
0
30
50
70
90
110
creatinine clearance (ml/min/1.73m2)


P = 0.0051
$Cl_{tot}$ (mL/min)
Creatinine Clearance (mL/min/1.73 $m^2$)
P = 0.2621
$C_{max}$ (ng/mL)
Creatinine Clearance (mL/min/1.73 $m^2$)


P = 0.9345
$T_{1/2}$ (h)
Creatinine Clearance (mL/min/1.73 $m^2$)
P = 0.0056
$AUC_{0-48}$ (µg)
Creatinine Clearance (mL/min/1.73 $m^2$)

Effect of food:

The pharmacokinetic parameters of memantine in plasma and in urine under fasting and fed conditions are summarized in the following Table:

**Table:**
**Pharmacokinetic Parameters (Mean ± SD) of Memantine Following a Single 20 mg Oral Dose Under Fasting and Fed Conditions in Geriatric Subjects with Normal Renal Function**

| *Parameter* | *Fasting State (n = 6)* | *Fed State (n = 6)* |
|---|---|---|
| $T_{1/2}$ (h) | 84.58 ± 12.51 | 95.39 ± 33.29 |
| $CL_{tot}$ (mL/min) | 136.8 ± 37.6 | 124.8 ± 51.3 |
| $CL_r$ (mL/min) | 150.4 ± 61.5 | 109.2 ± 27.1 |
| $A^e$0-48 (µg) | 7217 ± 3017 | 5318 ± 1200 |
| $AUC$0-t (ng h/mL) | 1645 ± 437 | 1593 ± 654 |
| $AUC$0-∞ (ng h/mL) | 2134 ± 608 | 2492 ± 905 |
| $C_{max}$ (ng/mL) | 23.12 ± 4.21 | 25.84 ± 4.29 |
| $T_{max}$ (h) | 6.7 ± 2.0 | 5.2 ± 2.0 |
| $V_d$ (L) | 968 ± 132 | 929± 73 |

Food caused an increase in mean AUC0-∞, Cmax, and T1/2 by 17%, 12%, and 13% respectively and a reduction in the mean amount of memantine excreted in urine during the interval of 0 to 48 hours post-dose by 26%. Mean AUC0-t remained relatively unchanged.

*Reviewer's Comment:*

- *It is not clear what the LOQ is for this study. Three validation reports (#ZA 001-92, ZA 002-92 and ZA 029-94) have been provided. They state that the methodology is the same as Analytical Report 610/7 in which the limit of quantitation is — g/ml in plasma and — ml in urine. The individual subjects plasma concentration lists that the LOQ is —. In the body of the study report at some place it is mentioned that the LOQ is —. No mention has been made on the LOQ in the urine. However, looking at the 3 validation reports mentioned above it appears to be —. The % CVs for inter or intra day validation have not been reported. It is difficult to ascertain the credibility of this study.*

*The study was conducted in 1994, but the report was amended to reclassify the renal impaired subjects as per the CrCL as per the FDA guidance. The amended reports analysis is appropriate provided credibility can be placed on the validation of the analytical report.*

- *The sponsor has clarified these issues. The LLOQ in plasma is — ng/ml in urine. The assay validation was based on methodology that was validated with a LLOQ of — ng/mL. In preparing the standard curve samples, the spiking*

*solution concentrations were based on the actual amount of reference material weighed at the time of the experiment and dilution scheme using fixed volume for each step as listed in the method. Hence, this LLOQ is lower than —ng/ml although the method does not change.*

*LLOQ of [redacted] in urine is within the standard curve range for the validated method.*

- *No quality control data was provided with the response.*

- *The control subjects had a mean CLr higher (150 ml/min) than the mean CLt (136 ml/min), which does not seem reasonable 3 out of the 6 subjects has CLr that was higher than the CLt.*

**Conclusions (cannot be reliably used for labeling)**

- Mild and moderate renal impairment caused reduction in total clearance by 17% and 33%, respectively, following a single 20 mg dose of memantine.
- Subjects with mild and moderate renal impairment had a mean increase in AUC0-∞ values by 14% and 39% relative to the subjects with normal renal function.
- The study does suggest that dosing adjustment may be needed for the moderate renal impairment group, however, the study conduct was not robust enough to include in the label. Another study with mild, moderate and severe renal impairment is ongoing and the sponsor plans to submit the report by mid 2004.

***Study: MEM 9601, NTI0015:*** *A Study of the Safety of single dose and Steady-State Pharmacokinetics of NEU 3004 in Healthy Volunteers and AIDS patients*

***Objective:***

The objectives of this study were to determine the safety and single dose and steady-state pharmacokinetics of NEU 3004 (memantine) in healthy volunteers and AIDS patients.

The study design is as follows:

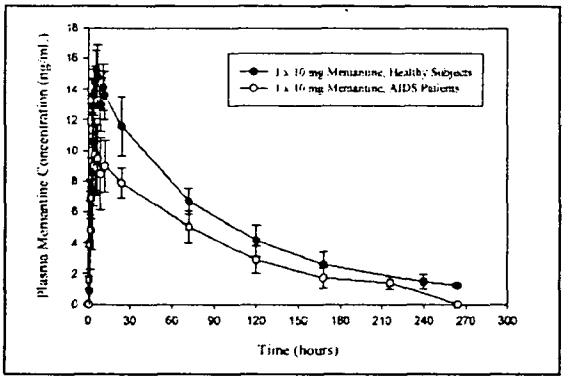
| Study Design | Open label, single dose followed by multiple dose |
|---|---|
| Study Population | N=16 subjects, 8 AIDS patients and 8 healthy subjects<br>Age: 18-45 years, mean age AIDS: 37.6 years, healthy: 32.2 years<br>Gender: AIDS: 7 males and 1 female<br>Healthy: 3 males and 5 females<br>Weight: mean AIDS 80.2 kg , mean healthy: 66.5 kg<br>Race: AIDS: 7 Caucasians, 1 Hispanic; healthy: 5 Caucasians, 3 Hispanic |
| Treatment Group | Initially each subject received a single oral dose of 10 mg memantine<br>Three weeks later subjects began the multiple dose escalation phase with 10 mg memantine once daily.<br>Subsequently the daily dose of memantine was increased at weekly intervals by 10 mg/day until a daily dose of 40 mg or the highest tolerated dose was reached. This dose was administered for 21 days.<br>AIDS patients received an additional 20 mg dose in the AM of the 22$^{nd}$ day, normal volunteers received 20 mg every 12 hours on the 22$^{nd}$ day.<br>This is given as follows:<br>Week 1: Single dose 1 x 10 mg memantine capsule<br>Week 4: 1 x 10 mg memantine capsule, once daily at 9 AM (10 mg/day)<br>Week 5: 1 x 10 mg memantine capsule every 12 hours at 9 AM and PM (20 mg/day)<br>Week 6: 2 x 10 mg memantine capsule in the morning (9 AM) and 1 x 10 mg memantine capsule at night (9 PM), daily (30 mg/day)<br>Weeks 7-9: 2 x 10 mg memantine capsule every 12 hours (40 mg/day)<br>Week 10: On Day 64, 2 x 10 mg memantine capsule at 9AM and 2 x 10 mg memantine capsules at 9 PM (40 mg/day) for healthy subjects or 2 x 10 mg memantine capsule at 9 AM for AIDS patients<br><br>Dose escalation occurred if the investigator judged that it was safe; otherwise, the subject was maintained on the highest tolerated dose until Day 64. |
| Dosage and Administration | Memantine provided as capsules<br>Overnight fast before single dose administration |

| | |
|---|---|
| Sampling: Blood | After Single Dose:<br>Healthy Subjects:<br>At 0 (predose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 9, 11, 12, 24, 72, 120, 168, 240, 264, 312, 360, and 504 hours post dose.<br>AIDS Patients:<br>At 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 9, 12, 24, 72, 120, 168, 216, 264, 312, and 504 hours post-dose.<br><br>After Multiple Doses:<br>Healthy Subjects:<br>On Day 64 at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 3.5, 4, 5, 6, 7, 9, 12, 12.5, 13, 14, 15, 16, 18, 20, 24, 72, 120, 168, 216, 264, 312, 360, 408, 456, and 504 hours post-dose.<br>AIDS Patients:<br>On Day 64 at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 9, 12, 24, 72, 120, 168, 216, 264, 312, 360, 408, 456, and 504 hours post-dose.<br><br>Additional blood samples were obtained for the determination of memantine trough (morning pre-dose) plasma concentrations on Days 29, 36, 43, 50, 57, 58, 60, and 62. |
| Urine | none |
| Feces | none |
| Analysis | for memantine samples<br>Lower Limits of Quantitation<br>Plasma<br>Memantine<br><br>Linear Range:<br>Plasma: Inter and Intraday precision<br>Quality control concentrations, ng/ml<br>All stability parameters given<br><br>Assay complete and acceptable |
| PK Assessment | AUC, Cmax, Tmax, t1/2, Cmin, Vdz/f, Css |
| Safety Assessment | Adverse events, Laboratory tests |

***Pharmacokinetic Results:***

After Single Dose:

The mean plasma concentration versus time profiles of memantine following a single 10 mg oral dose in healthy subjects and AIDS patients are presented in the following Figure. Plasma concentrations were below LOQ (— ng/ml) following the 264-hour plasma sample. The data showed 2 distinct peaks (at 6 and 11 hours in healthy subjects and 5, 7 and 12 hours in AIDS patients) and was observed in most subjects. Some subjects had 3 peaks. Higher plasma memantine concentrations were observed in healthy subjects than in AIDS patients.




The pharmacokinetic parameters of memantine following a single 10 mg dose in healthy subjects and AIDS patients are summarized in the following Table. Mean Cmax and AUC0-∞ values were reduced in AIDS patients by 35% and 32%, respectively relative to the values in healthy subjects.

**Table:**
**Pharmacokinetic Parameters (Mean ± SD) of Memantine Following a Single 10 mg Oral Dose in Healthy Subjects and AIDS Patients**

| *Parameter* | *Healthy Subjects (N=8)* | *AIDS Patients (N=8)* |
|---|---|---|
| $C_{max}$ (ng/mL) | 15.6 ± 1.15 | 10.2 ± 2.31 |
| $C_{max}$ (ng/mL) Wt Adjusted | 14.8 ± 1.3 | 11.7 ± 3.4 |
| $T_{max}$ (h) | 6.19 ± 1.19 | 6.00 ± 2.62 |
| $AUC_{0-24}$ (ng h/mL) | 289 ± 25.3 | 191 ± 36.8 |
| $AUC_{0-\infty}$ (ng h/mL) | 1413 ± 270 | 969 ± 237 |
| $AUC_{0-\infty}$ (ng h/mL) Wt Adjusted | 1342 ±263 | 1114 ± 330 |
| $T_{1/2}$ (h) | 68.7 ± 14.3 | 63.7 ± 12.5 |
| CL/F (L/h) | 6.06 ± 1.11 | 8.97 ± 1.94 |
| $V_{d/F\ (L)}$ | 584 ± 61.1 | 798 ± 109 |
| CL/Wt (L/h/kg) | 0.091 ± 0.013 | 0.114 ± 0.029 |
| $V_{d/wt\ (L/Kg)}$ | 8.79 ± 0.612 | 10.12 ± 1.89 |

After adjusting for weight differences and normalizing for a 70 kg subject, differences in mean Cmax and AUC0-∞ values were less pronounced, representing a 21% and 17% reduction in AIDS patients, respectively. Tmax and T1/2 were similar between the two groups. Another potential confounding factor could be drug-drug interactions with drugs used in AIDS patients.

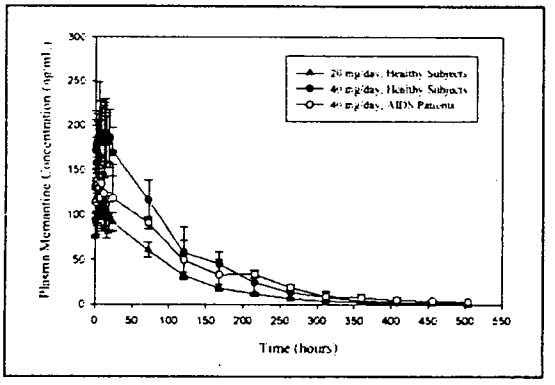
After Multiple Dose:

Following multiple oral doses of memantine in the healthy subjects for 64 days, 4 out of

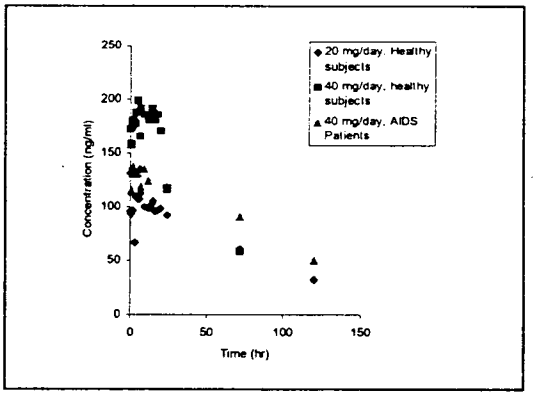
the 8 subjects had been escalated to the 40 mg/day dose. Data from one of these subjects were excluded from the pharmacokinetic analysis because subject was not compliant with the dosing regimen. Two subjects were only escalated to the 20 mg/day dose and another two subjects were escalated to the 30 mg/day dose. One of the two subjects receiving 30 mg/day, remained at this dose level only for Days 36-40 and was then returned to the 20 mg/day dose level for the remainder of the study. Thus, Day 64 pharmacokinetic data were available from 3 subjects at the 40 mg/day dose level, 1 subject at the 30 mg/day dose level and 3 subjects at the 20 mg/day dose level.

During the multiple dose phase of the study in the AIDS patients, 2 subjects dropped out of the study. Another subject was excluded because drug accountability showed that subject did not take many of the doses over Days 50 – 64 of the study. Three subjects completed dosing up to 40 mg/day. Another subject was escalated to 40 mg/day but was reduced to 20 mg/day on Day 56 through Day 64. A different subject received 40 mg/day through Day 50, stopped dosing from Days 51 – 55 and resumed dosing at 40 mg/day from Day 56 to Day 64. This subject was excluded from multiple dose pharmacokinetic analysis because he missed 5 days of dosing and had four consecutive missing concentrations (Day 62 trough and Day 64 at 0, 0.5, and 1 hour).

The mean plasma memantine concentrations on Day 64 following multiple dosing of 20 mg and 40 mg memantine in healthy subjects and 40 mg memantine in AIDS patients is shown in the following Figure.




(Profile 0-500 hours)




(Profile 0-150 hours, expanded)

On Day 64, healthy subjects received either 10 mg or 20 mg memantine at 9 AM and 9 PM while AIDS patients received 20 mg memantine at 9 AM. Healthy subjects who received 40 mg/day memantine had higher plasma concentrations over the 0 to 168 hour interval. Over the 216 through 504 hours post-dose interval the memantine plasma concentrations were similar in the normal subjects and AIDS patients who received the memantine 40 mg/day dose.

The steady-state pharmacokinetic parameters of memantine following dosing in the morning and evening of Day 64 in healthy subjects are presented in the following Tables for the 10 mg and 20 mg dose, respectively.

| **Table:**<br>**Pharmacokinetic Parameters at Steady-State (Mean ± SD) of Memantine Following 10 mg Oral Doses on the Morning and Evening of Day 64 in Healthy Subjects** | | |
|---|---|---|
| *Parameter* | *Morning Dosing (N=3)* | *Evening Dosing (N=3)* |
| $C_{max}$ (ng/mL) | 114 ± 15.5 | 107 ± 18.6 |
| $T_{max}$ (h) | 6.67 ± 0.578 | 4.67 ± 2.89 |
| $AUC_{0-12}$ (ng h/mL) | 1226 ± 167 | 1173 ± 179 |
| $C_{min}$ (ng/mL) | 88.1 ± 11.5 | 85.2 ± 13.1 |
| $C_{ss}$ (ng/mL) | 102 ± 13.7 | - |
| CL/F (L/h) | 6.85 ±0.936 | - |
| $V_{d/F}$ (L) | 637 ± 58.2 | - |
| $T_{1/2}$ (h) | - | 64.9 ± 4.07 |

| **Table:**<br>**Pharmacokinetic Parameters at Steady-State (Mean ± SD) of Memantine Following 20 mg Oral Doses on the Morning and Evening of Day 64 in Healthy Subjects** | | |
|---|---|---|
| *Parameter* | *Morning Dosing (N=3)* | *Evening Dosing (N=3)* |
| $C_{max}$ (ng/mL) | 211 ± 48.8 | 198 ± 37.3 |
| $T_{max}$ (h) | 5.33 ± 1.53 | 2.17 ± 1.44 |
| $AUC_{0-12}$ (ng h/mL) | 2191 ± 402 | 2201 ± 376 |
| $C_{min}$ (ng/mL) | 152 ± 36.3 | 170 ± 27.0 |
| $C_{ss}$ (ng/mL) | 183 ± 33.4 | - |
| CL/F (L/h) | 7.76 ± 1.54 | - |
| $V_{d/F}$ (L) | 669 ± 141 | - |
| $T_{1/2}$ (h) | - | 60.1 ± 8.35 |

Similar Cmax and AUC0-12 values were obtained following morning and evening dosing of memantine at steady-state in healthy subjects. Tmax was longer following morning dosing versus dosing in the evening. Cmax and AUC0-12 parameters increased proportionally with dose, t1/2 and CL remained unchanged.

The memantine pharmacokinetic parameters following dosing of 20 mg memantine on the morning of Day 64 in healthy subjects and AIDS patients are presented in the following Table.

| **Table:**<br>**Pharmacokinetic Parameters at Steady-State (Mean ± SD) of Memantine Following 20 mg Oral Doses on the Morning of Day 64 in Healthy Subjects and AIDS Patients** | | |
|---|---|---|
| *Parameter* | Healthy Subjects *(N=3)* | AIDS Patients *(N=3)* |
| $C_{max}$ (ng/mL) | 211 ± 48.8 | 161 ± 31.2 |
| $C_{max}$ (ng/mL) Wt adjusted | 197 ± 27 | 164 ± 42 |
| $T_{max}$ (h) | 5.33 ± 1.53 | 6.00 ± 3.00 |
| $AUC_{0-12}$ (ng h/mL) | 2191 ± 402 | 1547 ± 268 |

| | | |
|---|---|---|
| $AUC_{0-12}$ (ng h/mL) Wt Adusted | 2053 ± 184 | 1574 ± 375 |
| $C_{min}$ (ng/mL) | 152 ± 36.3 | 104 ± 9.67 |
| $C_{ss}$ (ng/mL) | 183 ± 33.4 | 129 ± 22.1 |
| CL/F (L/h) | 7.76 ± 1.54 | 11.0 ± 1.90 |
| $V_d$/F (L) | 669 ± 141 | 1281 ± 97.6 |
| $T_{1/2}$ (h) | 60.1 ± 8.35[a] | 82.3 ± 11.5 |

[a] Calculated following the evening dose on Day 64

Following morning dosing of 20 mg memantine on Day 64, mean Cmax and AUC0-12 values were lower in AIDS patients by 24% and 29%, respectively relative to the same measures in healthy subjects. After adjusting for weight differences, mean Cmax and AUC0-12 values were lower in AIDS patients by 18% and 23%, respectively. Terminal elimination half-life values were longer by 37% in the AIDS patients.

**Table:**
**Single Dose versus Multiple Dose Pharmacokinetic Parameters (Mean ± SD) of Memantine in Healthy Subjects and AIDS Patients at 40 mg/day**

| *Parameter* | Healthy Subjects Day 1 *(N=3)* | Healthy Subjects Day 64 *(N=3)* | Ratio Day 64/Day 1 | AIDS Patients Day 1 *(N=3)* | AIDS Patients Day 64 *(N=3)* | Ratio Day 64/Day 1 |
|---|---|---|---|---|---|---|
| $AUC^1$ (ng h/mL) | 1326 ± 230 | 2191 ± 402 | 0.826 | 872 ± 156 | 1547 ± 268 | 0.922 |
| CL/F (L/h) | 6.40 ± 1.23 | 7.76 ± 1.54 | 1.21 | 9.72 ±1.8 | 11.0 ±1.90 | 1.17 |
| $V_d$/F (L) | 589 ±44.5 | 669 ±141 | 1.13 | 830 ±135 | 1281 ± 98 | 1.58 |
| $T_{1/2}$ (h) | 65.4 ± 11.2 | 60.1 ± 8.35 | 0.931 | 59.9 ±11.4 | 82.3 ±11.5 | 1.39 |

1 AUC=total on Day 1, and AUC 12 on Day 64. The Day 64 AUC12 was divided by 2 to adjust for dose.

***Conclusions:***

- After a single dose mean Cmax and AUC0-∞ values were reduced in AIDS patients by 35% and 32%, respectively relatively to the values in healthy subjects, but these differences were substantially reduced (21 and 17% respectively) after correction of weight differences. AIDS subjects presented lower plasma concentrations and a larger Vd and CL compared to healthy subjects.
- At steady state mean Cmax and AUC12 values were lower in AIDS patients by 24% and 29%, respectively relative to the same measures in healthy subjects, however, after adjusting for weight differences, mean Cmax and AUC0-12 values were lower in AIDS patients by 18% and 23%, respectively. At steady state, the difference in Vd and CL were not substantially reduced (17 and 23% respectively) after weight adjustment and t1/2 was prolonged in AIDS patients.

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pages of trade

secret and/or

confidential

commercial

information

## BIOPHARMACEUTICS CLASSIFICATION SYSTEM

**Molecular Weight 215.77**
**Fine white to off-white powder**
**Ionization Constant: 10.3**

**Classification:** Based on the following information on solubility, permeability and dissolution, memantine can be classified as a BCS Class I drug, i.e. memantine is highly soluble, highly permeable and rapidly dissolving drug.

## SOLUBILITY:

The solubility studies were conducted at Forest Laboratories, Inc., Framingdale, NY.

pH-Solubility experiment: Memantine HCl was suspended in water to yield a saturated solution. The pH of the sample was altered using 0.1N NaOH or 0.1 N HCl. Samples were shaken on a wrist action shaker to attain equilibrium. Samples were then filtered and pH adjusted to about 12 with Sodium hydroxide. The precipitated free base was extracted into hexane and the solution was analyzed by —

Solubility in three buffers: The following solvents were used to conduct the solubility experiments: 0.1N HCl (pH 1.2), 0.05 M acetate buffer (pH 4.5) and 0.05 M phosphate buffer (pH 7).

Memantine HCl was suspended in the buffers to yield saturated solutions. Samples were shaken on a wrist action shaker for 3 hours at 37°C to attain equilibrium. Following filtration and suitable dilution drug solubility values were determined using a stability indicating — analysis.

The following Table lists the solubility values of memantine HCl (expressed as free base) at different pH values. The solubility values were approximately 40-45 mg/mL between pH's 2 and 9. The solubility declined steeply above pH 9.5.

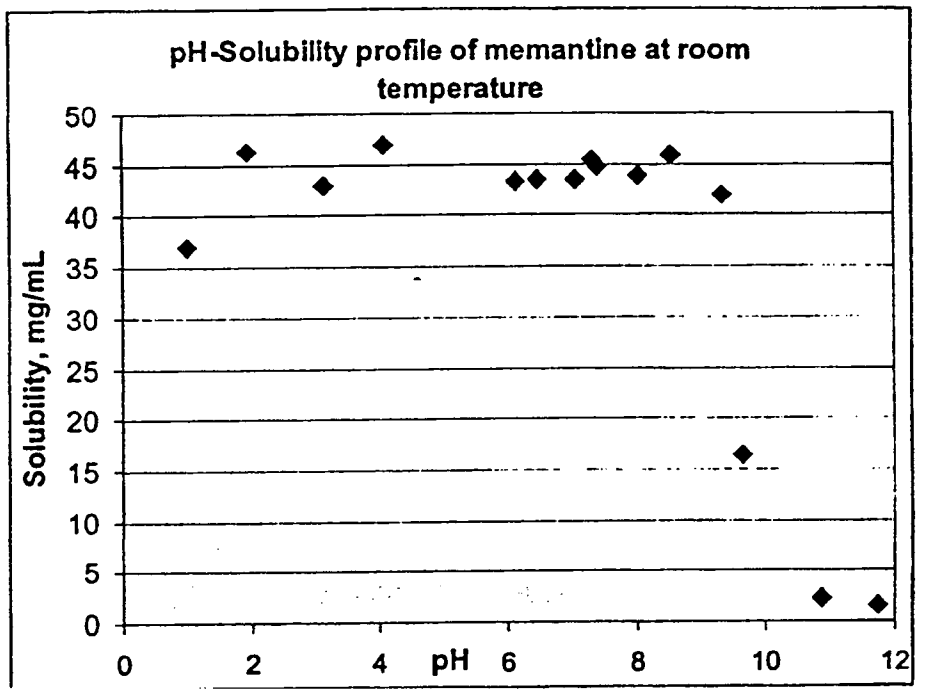
| pH | Solubility (mg/mL) |
|---|---|
| 1.01 | 37.0 |
| 1.96 | 46.4 |
| 3.14 | 43.1 |
| 4.0 | 47.0 |
| 6.14 | 43.4 |
| 6.49 | 43.5 |
| 7.07 | 43.6 |
| 7.33 | 45.5 |
| 7.41 | 44.8 |
| 8.03 | 43.9 |
| 8.55 | 45.9 |

| | |
|---|---|
| 9.33 | 41.9 |
| 9.64 | 16.4 |
| 10.88 | 2.3 |
| 11.74 | 1.6 |

The following Table lists the solubility values of memantine HCl at pH's 1.2, 4.5 and 7.0 at 37C

| pH | Solubility (mg/mL) |
|---|---|
| 1.20 | 31.2 ± 2.6 |
| 4.50 | 36.7 ± 0.7 |
| 6.99 | 38.6 ± 0.1 |

The pH solubility profile is shown in the following figure:




***Conclusion:***

Over the pH range 2-9, the solubility of memantine HCl was observed to be about 40-45 mg/mL. At pH's lower than 2 and higher than 9.5, the solubility tended to decrease. The solubilities in the three buffers were similar to that observed in the pH-solubility profile.

According to the BCS, a drug substance is classified as highly soluble, if the highest strength is soluble in less than 250 mL of aqueous media over the pH range 1-7.5. The highest dose of memantine tablet formulation is 20 mg. If this dissolves in 250 mL, it means that the resultant drug concentration would be 0.08 mg/mL. The solubility values of memantine HCl were significantly higher (40-45 mg/mL) than this concentration.

**PERMEABILITY:**

Although an absolute bioavailability study was conducted with memantine, the results were not realistic, showing absolute bioavailability of 149%, 120% and 97% with the 10, 20 and 40 mg tablets of memantine. Hence, in vitro permeability studies were conducted to show high permeability of memantine.

The permeability studies were conducted by .

Caco-2 cells were plated on . The surface area of the monolayer of the Caco-2 cells was 4.71 $cm^2$. Pemeability studies were conducted in Hank's balanced salt solution (HBSS) containing 10 mM HEPES buffer at 37°C and 50 oscillations per min. Volumes in the apical and basolateral compartments were 1.5 mL and 2.6 mL, respectively. Permeability studies were performed in triplicate at pH 6.8 and sampled over 60 min for the two higher donor concentration studies and 120 min for the lowest donor concentration studies. Samples were collected at 10, 20, 30, 40, 50 and 60 minutes. At each time point, the entire volume from the compartment (either receiver or donor) was collected and then, replaced by a fresh buffer. The pKa of memantine is about 10.3. It means, the ionization state of memantine would be unchanged between pH's 5.5 to 7.5 (solubility was the same in this pH range). Therefore, the permeability experiments were conducted only at one pH assuming similar permeabilities at pH's 5.5 and 7.5.

Apical to basolateral (AP-BL) and basolateral to apical (BL-AP) permeability values of memantine HCl were assessed at 1.6 µg/mL, 16 µg/mL, and 160 µg/mL (i.e., 1/100, 1/10, 1-fold of the maximum dose of 40 mg per 250 mL) at pH 6.8, along with 0.584 mM metoprolol and 25 µM fluorescein.

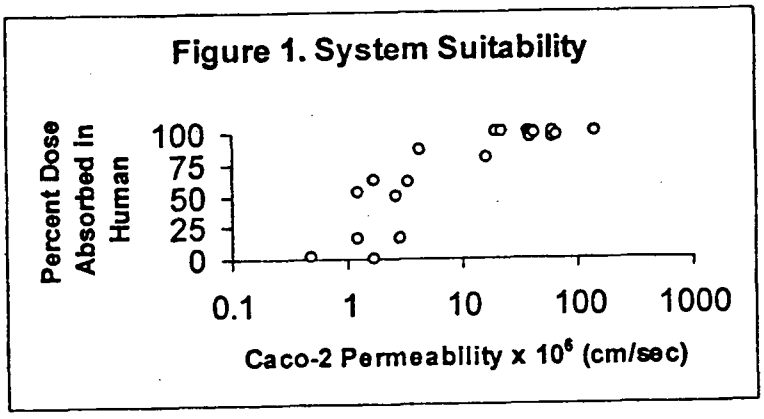
Fluorescein was used as a non-radioactive probe to ascertain the monolayer integrity. Some monolayers, after the transport studies of memantine HCl and fluorescein were subjected to monolayer integrity analysis by subsequent $^{14}C$-mannitol permeability measurements.

Since fluorescein was used as a primary low permeability marker for the memantine studies, a parallel study measured the AP-BL permeability of 25 µM fluorescein and 2 µM $^{14}C$ -mannitol, simultaneously. The permeabilities of fluorescein and $^{14}C$- mannitol were 4.51 (± 0.63) x $10^{-6}$ cm/sec and 2.07 (± 0.18) x $10^{-6}$ cm/sec, respectively. These values are consistent with previously reported values.

Parallel control studies involving the efflux of $^{3}$H-vinblastine were performed (along with $^{14}$C-mannitol) in both directions, to show P-gp activity. The donor concentration was 20 nM. AP-BL permeability of $^{3}$H-vinblastine was 4.15 (± 0.22) x $10^{-6}$ cm/sec and BL-AP permeability was 10.5 (± 0.3) x $10^{-6}$ cm/sec, suggesting efflux system was active in these cells. These values are consistent with previously reported values.

System suitability was illustrated by 20 model drugs as shown in the following Table and Figure. The figure shows the relationship between Caco-2 permeability and the percent dose absorbed (Reference: Lentz and Polli et al. International Journal of Pharmaceutics 200 (2000) 41-51 for 15 compounds and Dr. Jim Polli's laboratory for the other 5).

| Compound | AP-to-BL permeability × $10^{6}$ (cm/s) | Percent Dose Absorbed | Compound | AP-to-BL permeability × $10^{6}$ (cm/s) | Percent Dose Absorbed |
|---|---|---|---|---|---|
| Alendronate | 0.479 ± 0.045 | 1.2 | Chlorpheniramine | 16.0 ± 1.9 | 80 |
| Ranitidine hydrochloride | 1.23 ± 0.06 | 52 | Nicardipine | 19.8 ± 0.7 | 100 |
| Acyclovir | 1.24 ± 0.24 | 16 | Aspirin | 22.2 ± 0.9 | 100 |
| Cimetidine | 1.71 ± 0.08 | 62 | Indomethacin | 38.4 ± 2.2 | 100 |
| Bupropion hydrochloride | 66.4 ± 2.4 | 97 | Metoprolol | 40.0 ± 1.4 | 94.5 |
| PEG 4000 | 1.69 ± 0.06 | 0 | Dexamethasone | 40.3 ± 2.1 | 100 |
| Atenolol | 2.62 ± 0.17 | 50 | Diltiazem HCl | 42.4 ± 1.1 | 99 |
| Mannitol | 2.81 ± 0.16 | 16 | Theophylline | 61.0 ± 1.3 | 96 |
| Furosemide | 3.33 ± 0.07 | 61 | Lisuride | 61.1 ± 1.3 | 100 |
| Disopyramide | 4.24 ± 0.05 | 85.3 | Coumarin | 141 ± 6 | 100 |




Permeability was calculated using eq I:

$$P = \frac{dM/dt}{A * C_i} \qquad (1)$$

Where, $p$ is permeability, $dM/dt$ is rate of drug mass accumulation in the receiver compartment, $A$ is area of membrane, and $Cd$ is drug concentration in the donor compartment.

***Results:***

Regarding these studies of memantine HCl permeability assessment, the solubility of memantine HCl (expressed as free base) at pH 6.8 is well above 160 µg/mL. These concentration-dependent studies would suggest whether memantine is actively transported or effluxed.

The following Table shows that the permeability of memantine HCl was generally 30 to 40 x $10^{-6}$ cm/sec for all the concentrations (expressed as free base). The permeability was not concentration dependent or direction dependent (i.e., AP-BL vs. BL-AP), indicating passive permeability. In all the cases, the permeability of memantine HCl was greater than the permeability of metoprolol, indicating memantine HCl to be highly permeable.

| Memantine donor concentration | Memantine AP-BL Permeability x $10^6$ (cm/sec) | Metoprolol AP-BL Permeability x $10^6$ (cm/sec) | Memantine BL-AP Permeability x $10^6$ (cm/sec) | Metoprolol BL-AP Permeability x $10^6$ (cm/sec) |
|---|---|---|---|---|
| 1.6 µg/mL[a] | 34.3 (± 0.7) | 34.2 (± 0.10) | 31.4 (± 1.2) | 26.3 (± 0.8) |
| 16 µg/mL[b] | 44.1 (± 1.6) | 30.9 (± 1.2) | 34.6 (± 1.9) | 21.8 (± 0.1) |
| 160 µg/mL[c] | 40.5 (± 2.4) | 28.1 (± 1.2) | 32.3 (± 1.3) | 20.8 (± 0.5) |

[a] Fluorescein permeability in the AB-BL and BL-AP directions were 5.73 (± 0.47) and 6.10 (± 0.34) x $10^{-6}$ cm/sec, respectively, indicating competent monolayers.
[b] Fluorescein permeability in the AB-BL and BL-AP directions were 2.77 (± 0.43) and 2.69 (± 0.04) x $10^{-6}$ cm/sec, respectively, indicating competent monolayers. Additionally, after the AB-BL memantine and fluorescein transport studies, the permeability of mannitol was measured and was 1.80 (± 0.15) x $10^{-6}$ cm/sec.
[c] Fluorescein permeability in the AB-BL and BL-AP directions were 3.16 (± 0.29) and 3.23 (± 0.11) x $10^{-6}$ cm/sec, respectively, indicating competent monolayers. Additionally, after the AB-BL memantine and fluorescein transport studies, the permeability of mannitol was measured and was 1.92 (± 0.32) x $10^{-6}$ cm/sec.

***Conclusions:***

The permeability of memantine HCl across Caco-2 monolayers was passive and higher than metoprolol. There was no indication of involvement of any efflux system. The results indicate that memantine could be classified as a "highly permeable" drug according to the Biopharmaceutics Classification System guidance.

**DISSOLUTION:**

Dissolution Method:

| | |
|---|---|
| Apparatus: | USP I |
| Type: | Basket |
| Speed of Rotation: | 100 rpm |
| Media: | 0.1 N HCl, 0.1 N HCl with NaCl at pH 1.2, pH 4.5 acetate buffer, pH 6.8 phosphate buffer |
| Media Volume: | 900 mL |
| Temperature: | 37°C |
| Sampling Volume: | |
| Sampling Time: | 15, 30, 45 and 60 minutes |

The list of memantine tablet strengths used in this study

| Dose strength, mg/tablet | Lot Number |
|---|---|
| 5 | 5001 |
| 10 | 5006 |
| 15 | 5900 |
| 20 | 5011 |

The following Table lists the mean percent dissolved and RSD values (n=12) for the memantine tablets in four media (0.1N HCl, pH 4.5 acetate buffer pH 6.8 phosphate buffer and pH 1.2 NaCl/HCl). From the data it is evident that more than 90% is dissolved by the 15 minute time point.

***Conclusion:*** More than 90% is dissolved by 15 minutes. Hence, memantine tablets can be considered "rapidly dissolving".

**Table II : Mean percent dissolved values for various IR memantine formulations using USP I apparatus at 37°C (n=12)**

| Medium/Minutes | 5 mg tablets | | 10 mg tablets | | 15 mg tablets | | 20 mg tablets | |
|---|---|---|---|---|---|---|---|---|
| | Mean | RSD | Mean | RSD | Mean | RSD | Mean | RSD |
| **0.1 N HCl** | | | | | | | | |
| 15 | 95 | 2.2 | 96 | 2.3 | 101 | 2.5 | 101 | 1.8 |
| 30 | 95 | 1.8 | 95 | 1.8 | 102 | 2.8 | 100 | 1.3 |
| 45 | 95 | 2.4 | 95 | 2.0 | 102 | 2.7 | 99 | 1.4 |
| 60 | 94 | 2.3 | 95 | 1.7 | 100 | 2.6 | 99 | 1.1 |
| **pH 4.5 acetate buffer** | | | | | | | | |
| 15 | 101 | 3.5 | 101 | 3.5 | 100 | 1.4 | 99 | 1.2 |
| 30 | 101 | 4.3 | 99 | 3.7 | 99 | 1.7 | 99 | 1.3 |
| 45 | 100 | 3.6 | 99 | 4.1 | 99 | 1.8 | 98 | 1.6 |
| 60 | 99 | 3.6 | 98 | 3.9 | 98 | 1.6 | 98 | 1.8 |
| **pH 6.8 phosphate buffer** | | | | | | | | |
| 15 | 92 | 2.9 | 95 | 2.9 | 102 | 2.2 | 103 | 1.5 |
| 30 | 93 | 2.4 | 95 | 2.4 | 102 | 2.5 | 104 | 1.6 |
| 45 | 93 | 1.9 | 95 | 2.7 | 101 | 2.2 | 103 | 1.9 |
| 60 | 94 | 2.0 | 94 | 2.6 | 101 | 2.6 | 103 | 1.9 |
| **0.1 N HCl with NaCl** | | | | | | | | |
| 15 | 97 | 2.3 | 97 | 5.0 | 102 | 2.0 | 101 | 2.7 |
| 30 | 97 | 2.6 | 98 | 5.4 | 102 | 1.9 | 103 | 1.2 |
| 45 | 97 | 2.5 | 98 | 5.1 | 102 | 2.3 | 102 | 1.3 |
| 60 | 96 | 3.1 | 97 | 6.2 | 102 | 2.0 | 102 | 1.3 |

RSD = relative standard deviation

## DISSOLUTION SPECIFICATIONS

**Method:**

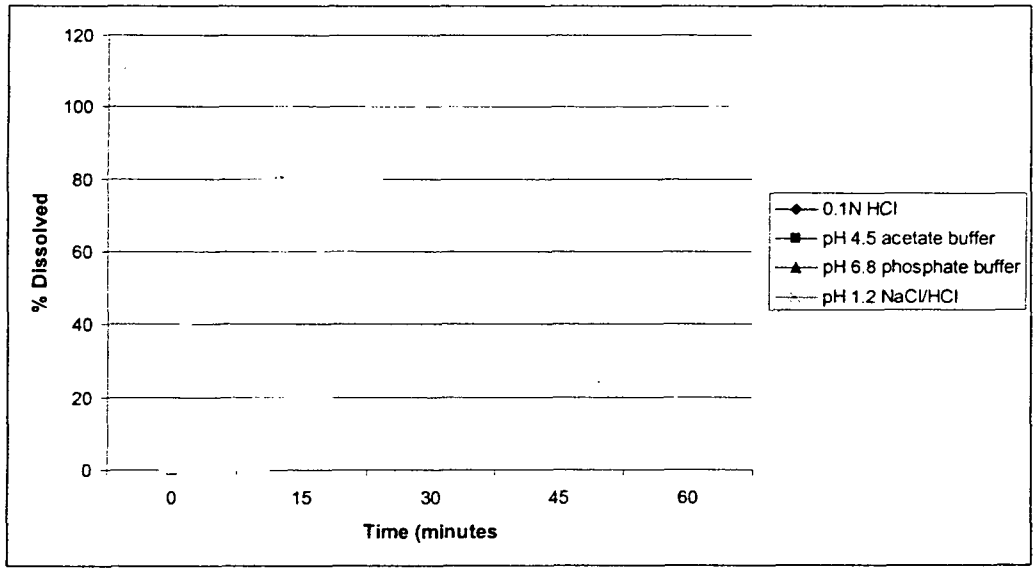
| | |
|---|---|
| Apparatus: | USP I |
| Type: | Basket |
| Speed of Rotation: | 100 rpm |
| Media: | 0.1 N HCl with NaCl at pH 1.2, |
| Media Volume: | 900 mL |
| Temperature: | 37°C |
| Sampling Volume: | |
| Sampling Time: | 15, 30, 45 and 60 minutes |

(Note: Only single point dissolution with sampling at 30 minutes is required for commercial drug testing)

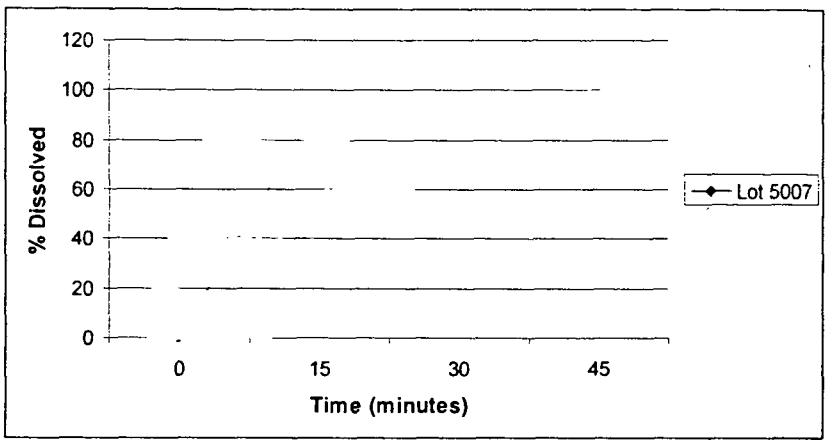
Q= — % at 30 minutes

**Effect of dissolution media and pH:**

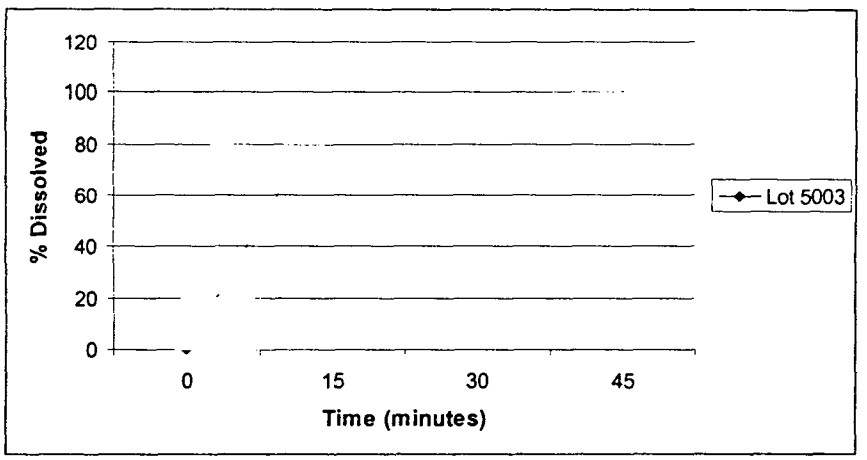
*The dissolution media tested at various pH were:* 0.1 N HCl, 0.1 N HCl with NalL at pH 1.2, pH 4.5 acetate buffer, pH 6.8 phosphate buffer.
More than 90% was dissolved in 15 minutes in each case, as shown in the figure below:




The dissolution profile for 10 mg tablet for the lot 5007 used in the pivotal BE study with the Forest product is shown below:




The dissolution profile for 5 mg tablet for the lot 5003 used in the pivotal clinical study MEM-MD-02 with the Forest product is shown below:




Justification for method:

Apparatus 1, 100 rpm was chosen by the sponsor

Justification for the Specifications:

The specifications were based on the 12 month controlled room temperature stability data and accelerated storage conditions.

N 21-487
Memantine HCl

***Conclusions:***

Based on the dissolution information provided dissolution specifuication of Q=__% in 30 minutes is acceptable

## 6.2 APPENDIX II

## SPONSOR'S PROPOSED LABEL

25 pages redacted from this section of the approval package consisted of draft labeling

## 6.3 APPENDIX III
## FILING AND REVIEW FORM

*Office of Clinical Pharmacology and Biopharmaceutics*
***New Drug Application Filing and Review Form***

General Information About the Submission

| | Information | | Information |
|---|---|---|---|
| NDA Number | N21-487 | Brand Name | NAMENDA |
| OCPB Division (I, II, III) | I | Generic Name | Memantine HCl |
| Medical Division | 120 | Drug Class | NMDA receptor antagonist |
| OCPB Reviewer | Veneeta Tandon | Indication(s) | Moderate to severe dementia of Alzheimer's Type |
| OCPB Team Leader | Ramana Uppoor | Dosage Form | 5/10/15/20 mg Film Coated Tablets |
| | | Dosing Regimen | Target dose 20 mg/day Starting dose 5 mg QD, then 10 mg/day (5 mg b.i.d), then 15 mg/day (5 and 10 mg as separate doses), and finally 20 mg/day (10 mg b.i.d.) Dose should be increased at 5 mg increments |
| Date of Submission | 12/31/02 | Route of Administration | Oral |
| Estimated Due Date of OCPB Review | 9/31/03 | Sponsor | Forest Laboratories |
| PDUFA Due Date | 10//31/03 | Priority Classification | 1S |
| I. Division Due Date | | | |

Background:
Memantine is an NMDA receptor antagonist and was first approved in Germany in 1978. As of June 30, 2002, this product has received marketing authorization in 42 countries. Memantine has been marketed under the tradename"AKATINOL" in 23 countries for the treatment of mild to moderate dementia syndrome. Merz Co. has also received registration for marketing memantine under the tradename "AXURA" for the treatment of moderate to severe Alzheimer's Disease. AKATINOL was voluntarily withdrawn from few countries.
20 PK studies have been submitted to support this NDA and 3 studies are ongoing.
The clinical trial formulation is different from the to-be-marketed formulation.

Clin. Pharm. and Biopharm. Information

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | | | |
| Tabular Listing of All Human Studies | X | | | |
| HPK Summary | X | | | |
| Labeling | X | | | |
| Reference Bioanalytical and Analytical Methods | X | | | Validation provided |
| I. Clinical Pharmacology | | | | |
| Mass balance: | X | 2 | | • 5 mg t.i.d.<br>• one pilot study |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| Healthy Volunteers- | | | | |
| single dose: | X | 4 | | • 10, 20 and 40 mg oral<br>• 30 and 40 mg i.v.<br>• penetration of memantine in CSF<br>• Penetration of memantine in sweat |

| | | | | |
|---|---|---|---|---|
| multiple dose: | X | 3 | | • 5, 10 and 20 t.i.d. for 12 days,<br>• 5,10, 20 mg b.i.d<br>• to study effect of urine pH and flow on renal clearance<br>• effect of memantine on EEG |
| *Patients-* | | | | |
| single dose: | | | | |
| multiple dose: | X | 1 | | Determination of memantine in lacrimal fluid |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | X | 1 | | • 5, 10, 20 and 40 mg |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | X | 1 | | • With Hydrochlorthiazide |
| In-vivo effects of primary drug: | X | | | |
| In-vitro: | X | | | • Human liver microsomes<br>• Is memantine a substrate of P-glycoprotein |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | X | 1 | | |
| hepatic impairment: | | | | |
| AIDS patients | X | 1 | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | X | 1 | | 10, 20 and 40 mg |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | X | 5 | | Compared to SR formulations |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | X | 1 | | • Combined with a BE Study, but with Merz formulation<br>• Ongoing with Forest Formulation |
| **Dissolution:** | X | | | Three media, all strengths |
| **(IVIVC):** | | | | |
| **Bio-waiver request based on BCS** | X | | | Request for waiver between IR tablet and solution based on dissolution and BCS class I |
| **BCS class** | X | | | Caco2 permeability, solubility and Dissolution data provided |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | Deferral request |
| **Literature References** | 9 | | | |
| **Total Number of Studies** | | 20 | 20 | |

| | | | | |
|---|---|---|---|---|
| Filability and QBR comments | | | | |
| **II.** | **"X" if yes** | **Comments** | | |
| **III. Application filable ?** | **X** | Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one? | | |
| **IV. Comments sent to firm ?**<br>**V.** | **X** | Comments have been sent to firm (or attachment included). FDA letter date if applicable.<br>• **Please provide PK summary Vol number 71 electronically.**<br>• **Please provide data sets (as SAS transport files) for the pharmacokinetic parameters (individual values) with the corresponding subject demographics from the studies that the pharmacokinetic information in the label is based on.**<br>• **Please provide a pooled analysis across all PK relevant studies for effect of age and gender.**<br>• **Does the sponsor have any data for the PK of memantine in Alzheimer patients** | | |
| **QBR questions (key issues to be considered)** | • **Are the analytical methods appropriately validated?**<br>• **Does the submitted data support the proposed label?**<br>• **Are the dosing recommendations appropriate from a PK point of view?**<br>• **Is the PK of memantine adequately characterized?**<br>• **Are special populations adequately studied?**<br>• **Are appropriate BE links provided?**<br>• **Is this a BCS Class I drug?** | | | |
| **Other comments or information not included above** | • **A BE study comparing the tablets manufactured by Forest Lab and Merz Co. is ongoing. This also evaluates the food effect of the Forest Formulation**<br>• **Another DDI study between memantine and donepezil is also ongoing.**<br>• **The ongoing studies will be made available at the 120-day update submission.**<br>• **No specific study has been done for effect of gender, however, information has been provided from other studies, where both genders were included**<br>• **No specific study has been done for effect of age, however, in BE studies using SR and IR formulations elderly were included in the study. The maximum age studied was 69 yrs. In patients with renal impairment the maximum age studied is 77yrs.**<br>• **PK study in Alzheimer Disease patients has not been conducted. This drug would be given in the geriatric population, but appropriate age analysis has not been conducted**<br>• **If filed, a BCS consult during review may be needed and a DSI audit of the BE study may be needed** | | |
| **Primary reviewer Signature and Date** | **Veneeta Tandon, Ph.D** | | | |
| **Secondary reviewer Signature and Date** | **Ramana Uppoor, Ph.D** | | | |

***CC: NDA 21-487, HFD-850(Electronic Entry or Lee), HFD-120(CSO), HFD-860(Uppoor, Sahajwalla, Mehta)***

## 6.4 APPENDIX IV

## BCS REVIEW BY DR. DONNA VOLPE

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Rockville, MD 20857

# MEMORANDUM

**Date**: September 30, 2003

**To**: Veneeta Tandon
Division of Pharmaceutical Evaluation I

**From**: Donna A. Volpe, Ph.D.
Division of Product Quality Research

**Subject**: BCS Permeability of Memantine

BCS Guidance – *In Vitro* Permeability Evaluation

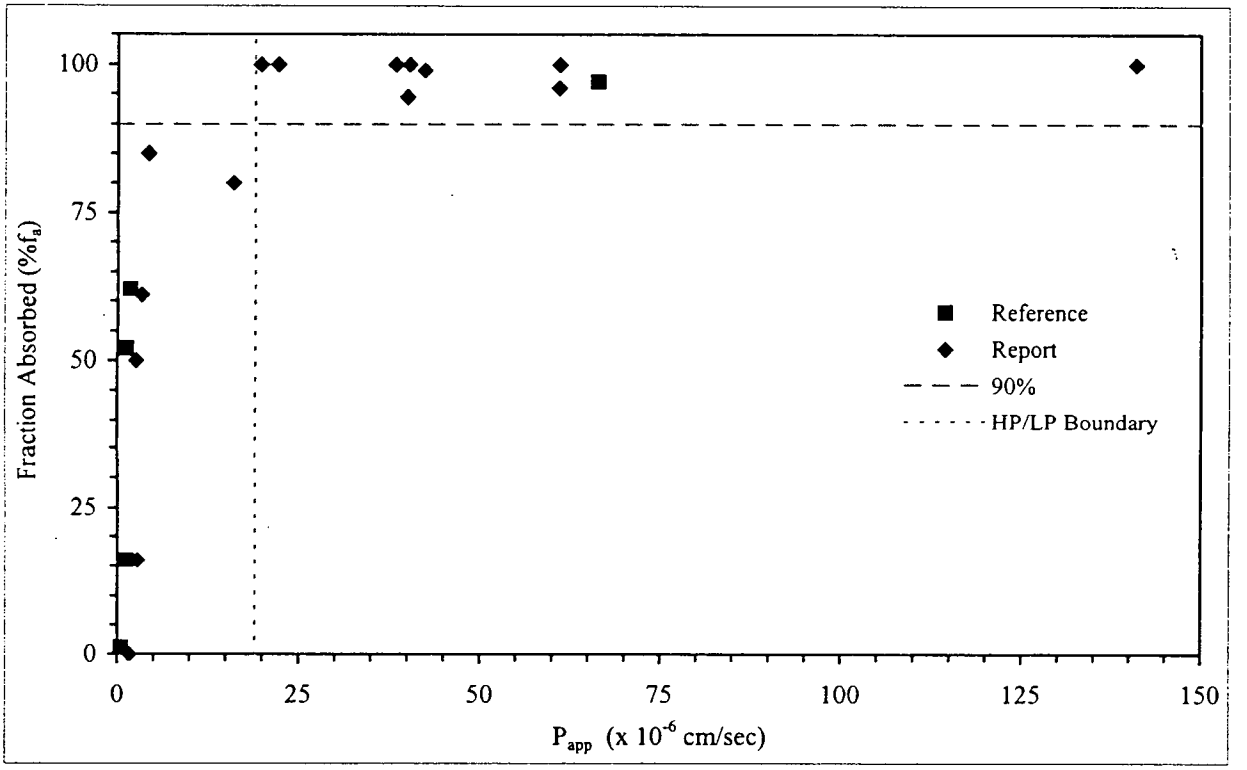
The BCS guidance sets for methods and specifications for the use of in vitro cell culture assays to classify drug permeability.

- Method suitability is demonstrated by a rank-order relationship between model drug permeability values and the extent of drug absorption data in human subjects using a sufficient number of model drugs (20). This relationship should allow precise differentiation between drug substances of low and high intestinal permeability attributes.
- For a given test method with set conditions, the selection of a high permeability internal standard with permeability in close proximity to the low/high permeability class boundary is utilized in the classification of a test drug substance.
- Cell culture methods are appropriate for only those drugs having passive permeability. This is demonstrated *in vitro* by a lack of dependence of the measured *in vitro* permeability on initial drug concentration (*e.g.*, 0.01×, 0.1×, and 1× the highest dose strength dissolved in 250 mL) and transport direction (*e.g.*, no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected) using a suitable *in vitro* cell culture method that has been shown to express known efflux transporters (*e.g.*, P-glycoprotein).

Permeability Classification of Memantine Hydrochloride

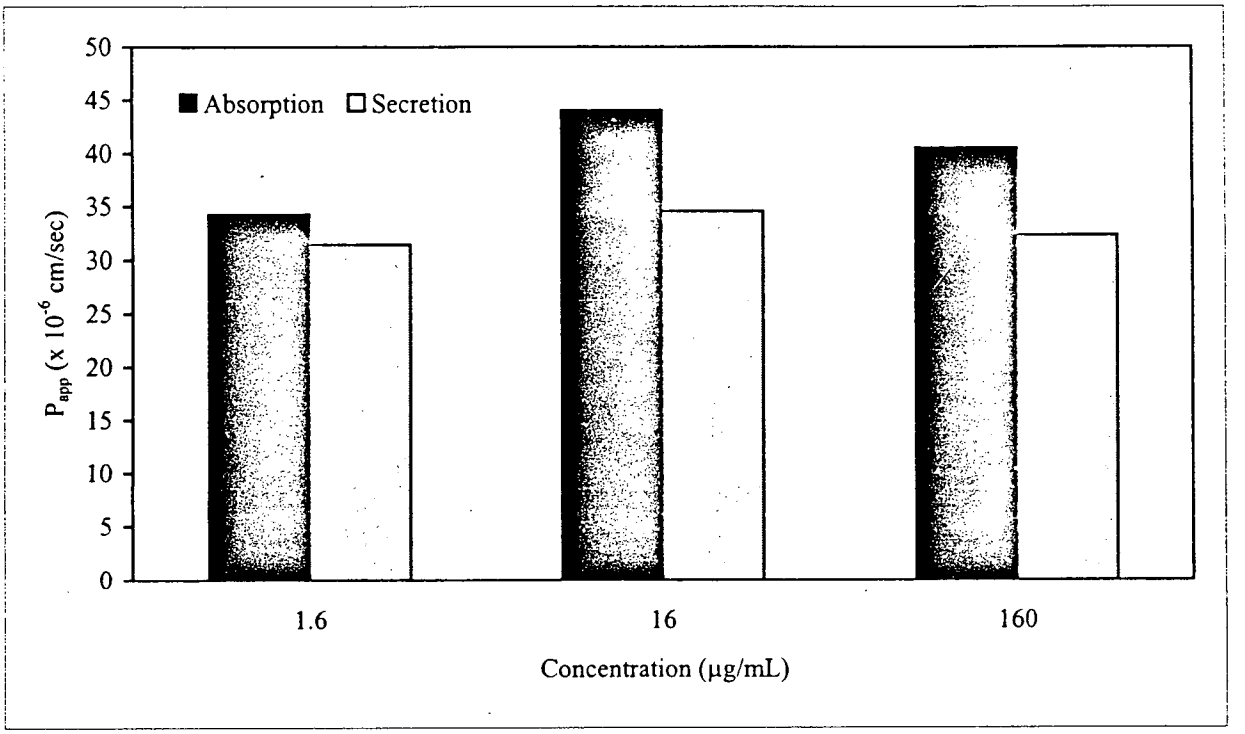
Forest Laboratories, Inc. (Inwood, NY) submitted data supporting the classification of memantine as a highly permeable drug substance. The study was completed by [redacted] ) using an accelerated Caco-2 permeability assay developed in his laboratory.

Method suitability was demonstrated by a combination of data on 15 drugs from a previous reference [Lentz *et al.* Int. J Pharm. 200:41-51, 2000] and 5 additional drugs for the Forest project. The graph below shows that the method can distinguish between high and low permeability compounds with nicardipine and aspirin at the high/low boundary with $P_{app}$ values of 19.8 and 22.2 $\times$ $10^{-6}$ cm/sec, respectively, both having 100% absorption in humans. However, metoprolol (40.01 $\times$ $10^{-6}$ cm/sec, $f_a$ = 95%) was used as the high permeability which may cause misclassification of compounds in the 20 to 40 $\times$ $10^{-6}$ cm/sec range.




The experiments to evaluate the permeability of memantine utilized metoprolol and fluorescein as the high and low permeability internal standards, respectively. Mannitol was utilized as a marker of monolayer integrity. The $P_{app}$ values for these three standards were comparable to previous experiments in the laboratory.

Memantine was evaluated at three concentrations based upon a maximum dose of 40 mg in 250 mL (i.e., 1.6, 16 and 160 µg/mL). Transport was evaluated in both the absorptive (apical-to-basolateral) and secretive (basolateral-to-apical) directions.




The experiments with fluorescein and mannitol demonstrated competent and intact cell monolayers. The permeability for metoprolol ranged from 31.4 to 34.6 × $10^{-6}$ cm/sec. Transport experiments with vinblastine, a substrate for P-glycoprotein efflux, confirmed the presence of P-glycoprotein on the cells as its secretive transport (10.5 × $10^{-6}$ cm/sec) was 2.5-fold higher than in the absorptive direction (4.15 × $10^{-6}$ cm/sec).

This study has shown that memantine is passively absorbed as there is no significant changes in permeability at the three concentrations. In addition, memantine is not subject to efflux as its secretive transport is not greater than absorption. Memantine's $P_{app}$ is greater than the high permeability standard metoprolol, thus classifying it as a high permeability drug.

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/s/

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Veneeta Tandon
10/2/03 10:43:25 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
10/2/03 11:27:38 AM
BIOPHARMACEUTICS