CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-487

Clinical Pharmacology and Biopharmaceutics Review

OCT - 2 2003

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Memantine HCl
NDA:	21-487
PRODUCT (Brand Name):	NAMENDA
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	5, 10, 15 and 20 mg
INDICATION:	Moderate to severe dementia of Alzheimer's type
NDA TYPE:	1S
SUBMISSION DATES:	12/19/02, 4/11/03, 3/5/03, 3/24/03, 8/8/03, 8/13/03, 8/28/03
SPONSOR:	Forest Laboratories Inc
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCPB DIVISION:	DPE I, HFD 860
OND DIVISION:	HFD 120

1.0 EXECUTIVE SUMMARY

Forest Laboratories Inc. seeks approval for NDA 21-487 (memantine HCl) tablets in the strengths of 5, 10, 15 and 20 mg for the treatment of moderate to severe dementia of the Alzheimer's type (DAT). Memantine HCl is a moderate affinity uncompetitive NMDA receptor antagonist unlike other drugs for the treatment of DAT that are mainly acetylcholine esterase inhibitors. The recommended starting dose of memantine is 5 mg once daily. The recommended target dose is 20 mg/day. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day). The minimum recommended

interval between dose increases is one week. Memantine can be taken without regard to food.

The sponsor has submitted 23 in vivo pharmacokinetic studies to support the pharmacokinetics of memantine, out of which 19 studies have been reviewed. Out of these studies only 5 had adequate assay validation reports as per the FDA guidelines on Bioanalytical Validation (these include bioequivalence evaluation, food effect, two drug-drug interaction studies and general pharmacokinetics after a single dose). All other studies had some aspect of the assay validation that was not done as per the current standards. The pharmacokinetic studies conducted earlier in the drug development used — methodology where as the more recent studies utilized — method for the analysis of plasma and urine samples. The sponsor states that some of the assay validation was not per the FDA guidelines on Bioanalytical Validation, but were based on the ICH guidelines at that time. A few studies lacked the quality control runs but had the calibration curves. Some of these studies (not considered pivotal) with less stringent analytical validation reports were accepted based on the following reasons: (a) no drift in the data from assays that had adequate quality control data and used the same methodology, (b) pharmacokinetic parameters across studies at the same dose level had similar parameter values using the same — methodology, (c) parameter values obtained for studies at same doses using the — method were very similar to those obtained using — method.

Some review issues have been identified that impact the quality of the data submitted for review. Key limitations from some studies are:

- One well conducted study and two other pilot studies suggest that the absolute bioavailability of memantine is greater than 100%. The reason for this is not clear.
- The study conducted in the mild and moderately impaired renal patients did not have adequate quality control data to assess the adequacy of the study. Three out of six subjects in the control group had CLr values that were greater than the CLt. Subjects with moderate renal impairment showed a 39% increase in exposure as compared to the normal subjects. Due to the inadequacy of the study, the results from this study cannot be used to propose dosage reduction in subjects with moderate renal impairment. —
- Adequate characterization of the extent of renal elimination of memantine has not been elucidated due to conflicting results from 3 studies. A lack of study in hepatic impaired subjects is not justified based on the data provided.
- There is inadequate representaion of the elderly population in the traditional pharmacokinetic studies. There were only 6 subjects that were ≥ 65 years across all pharmacokinetic studies with the highest age of 71 years. The mean age of Alzheimer's patients is >75 years. However, there is reasonable pharmacokinetic data in this age group in Phase 3 clinical trials.
- A good estimation of accumulation cannot be obtained from the multiple dose studies as plasma samples were not taken on Day 1 of the Study. Assuming linear pharmacokinetics the accumulation factor after multiple doses has been predicted. A multiple dose study with the proposed dosing regimen (titrated regimen with a

starting dose of 5 mg/day and escalated on weekly basis up to 20 mg/day) has not been conducted. Multiple dose study has been conducted with BID dosing of 1x10 mg memantine for 18 days (20 mg/day)

Dosing adjustments may be needed for the following populations/situations:

(a) Subjects with renal impairment may show an increase in exposure as compared to the normal subjects. Dose reduction may be necessary, although adequate data is not available at this time

(b) Diet, drugs or disease states (such as renal tubular acidosis or severe infection of the urinary tract) that alter the urine pH to make it alkaline can reduce the clearance of the drug. Caution should be exercized in these situations.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE-I) has reviewed NDA 21-487. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view provided that the sponsor addresses the comments and Phase IV recommendations and agrees with the Agency's label recommendations. The labeling changes have been made to reflect the accuracy of the results obtained or to delete information from studies that were not conducted adequately.

The Phase IV Commitment recommendations on page 4 and labeling comments outlined in the Detailed Labeling Recommendation section of the review on page 46 should be conveyed to the sponsor.

The following comments should also be conveyed to the sponsor:

- For future NDA applications, the sponsor should have adequate assay validation reports as per the FDA guidance on Bioanalytical Method Validation submitted along with each study report. Any deviations from the validated method, should be clarified within the study report. All studies should have their own standard curves and quality control data for the analytical runs.
- CYP 450 inhibition studies with memantine have been conducted with liver from only one donor. In future such studies should be conducted with more than one donor as there can be large variability in CYP enzymes in livers from different donors and one donor may not represent this. Further all CYP isoenzymes may not be expressed in one donor. No information has been provided on the induction potential of memantine.
- When the dosing recommendations for the memantine tablets is to give them in divided doses with a maximum of 20 mg/day (as 10 mg BID), it is not clear why the sponsor would propose to market the 15 and 20 mg tablet strengths. Please justify the marketing of these two strengths.

1.2 PHASE IV COMMITMENTS

- The ongoing renal impairment study should be submitted within 1 year from the date of approval and the label should be modified based on the results of the study.
- About 57-82% of memantine is eliminated intact in the urine. This shows that about 18-43% of memantine is eliminated through the metabolic route. The extent of renal elimination of intact memantine is not clear at this time due to conflicting results from the studies, the sponsor should conduct a study in subjects with moderate hepatic impairment compared to normal subjects. This aspect could be addressed if there are adequate number of hepatic impaired subjects in the clinical trials.
- The sponsor should evaluate the induction potential of memantine.

/S/ 10/2/03

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D. /S/ 10/02/03

2.0 TABLE OF CONTENTS

APPEARS THIS WAY
ON ORIGINAL

3.0 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The sponsor has submitted 23 in vivo pharmacokinetic studies to support the pharmacokinetics of memantine, out of which 19 studies have been reviewed. Out of these studies only 5 had adequate assay validation reports (these include bioequivalence evaluation, food effect, two drug-drug interaction studies and general pharmacokinetics after a single dose), all other studies had some aspect of the assay validation that was not as per the current FDA guidelines. The sponsor states that some of the assay validation was not per the FDA guidelines on Bioanalytical Validation, but were based on the ICH guidelines at that time. A teleconference was set up to discuss the assay validation report and missing information from the report from numerous studies. The sponsor was requested to respond to these additional requests and clarifications regarding the assays. The PK studies conducted in the early 1990's used —— ' as the assay validation method. Through out the studies numerous limits of quantitation were reported, with not adequate quality control data for some studies. The studies conducted in the later 1990's used —— as the assay methodology and were adequately validated as per the current FDA standards. The sponsor clarified some of the assay validation concerns in response to the teleconference. Some studies (that were not considered pivotal) that did not have quality control data but had data on standard curves that were generated each day of the analysis, were accepted based on (a) no drift in the data during the duration of the assay from studies that had quality control and used the same methodology (b) pharmacokinetic parameters across studies at the same dose level had similar parameter values, (c) pharmacokinetic parameters from the studies evaluated by the methodology were similar to those obtained by the —— methodology.

The findings from clinical pharmacology and biopharmaceutics section is as follows:

Exposure-Response for Efficacy or Safety:

Efficacy: No exposure-response relationship was observed for efficacy. Relationship between exposure and the clinical endpoint Severe Impairment Battery (SIB) was evaluated in one study. Results showed that subjects with higher plasma concentrations infact had the most mean worsening of cognition. No clear trend was observed with the plasma concentrations and mean worsening of cognition.
Safety: No relationships were observed between adverse events and exposure. Dizziness was the only adverse event that appeared to be dose related and was highest in the 40 mg dose group, which is not the proposed dose for the treatment of dementia of the Alzheimer's type.

General Pharmacokinetics (ADME characteristics) of memantine:
Absorption:

- Memantine appears to be highly absorbed with absolute bioavailability greater than 100% (from two studies). The reason for this is not clear. Various postulates have been highlighted in the individual study report.

- Tmax ranges from —— hours.
- There is no carrier-mediated transport for memantine.

Distribution:

- In vitro protein binding is 42-45%
- Volume of distribution is 9-11 L/kg suggesting extensive distribution.

Metabolism:

- Memantine is a low extraction ratio drug.
- The predominant route of memantine metabolism is via hydroxylation to form 1-amino-3- hydroxymethyl-5-methyladamantane (MRZ 2/373, 11-hydroxy memantine), 1-amino-3,5-dimethyl-7- hydroxyadamantane (MRZ 2/544, 7-hydroxy memantine), and MRZ 2/374 (6-hydroxy memantine). Other routes of metabolism are N-oxidation and conjugation. Quantitative estimation of these metabolites has not been conducted in the PK studies. The metabolites do not have NMDA receptor antagonist activity.
- The CYP isoenzymes do not play a role in the metabolism of memantine

Elimination:

- The half-life ranges from 57-95 hours across studies.
- Memantine is eliminated by both renal and non-renal routes. The extent of renal elimination is not very clear because of conflicting results from various studies. From a radiolabeled study one subject showed that 68% of the radioactivity was due to intact memantine with two other components accounting for 15% and 17% of the radioactivity. Other two studies showed that renal clearance amounted to about 90% and 50% respectively, of the total clearance in the two studies.
- The renal elimination of memantine is in part due to active tubular excretion.
- Memantine shows pH dependent tubular reabsorption. The renal clearance reduces by approximately 80-87% with alkaline urine conditions.

Single dose and multiple dose pharmacokinetics:

- Single doses of 1x 10 mg and 2 x 10 mg memantine have been evaluated. PK parameters appear to be consistent across studies.
- No PK study has been conducted with the proposed dosing regimen. With studies closest to the proposed regimen, (Study 1: 1x10 mg QD for 4 days followed by 1x10 mg BID for 18 days followed by 2x10 mg for 1 day; and Study 2: where 5 mg was given for 3 days, followed by 1x 10 mg QD for 4 days , followed by 2x 10 mg QD for 12 days; Study 3: where 1x 10 mg QD was given for 5 days followed by 1x 10 mg BID for 20 days), accumulation cannot be determined because blood samples were not taken on Day 1. In another study with TID dosing, an accumulation factor of 15 was observed. Based on linear pharmacokinetics, an accumulation factor of 10 is predicted upon multiple dosing.
- Steady state is reached within 13-16 days.

Dose proportionality:

No robust study is available to assess dose proportionality. The crossover study designed to assess dose proportionality in the dose range of 10-40 mg had plasma levels that were close to the LLOQ at the lowest dose, although the results from a power analysis show

that the pharmacokinetic parameters are proportional in the dose range of 10-40 mg. A second parallel study showed that doses are approximately proportional in the range of 5-40 mg.

Pharmacokinetics in patients:

No pharmacokinetic studies have been conducted in patients with Alzheimer's disease. Comparison of steady state plasma concentrations from clinical trial to the concentrations observed in healthy volunteers in the pharmacokinetic studies show some what comparable concentrations, although the absolute values were higher in patients. This also could be because (a) no pharmacokinetic study in the healthy volunteers was conducted with the proposed regimen and (b) the size of the population (healthy) is small. (c) Patients were generally older compared to healthy volunteers in pharmacokinetic studies.

Special Populations:

Renal Impaiment: Study was conducted with mild and moderate renal impaired subjects, but assay validation was not adequate. Results showed that in the moderate impaired subjects there was 33% reduction in CL/F and a 39% increase in AUC0-∞.

Hepatic Impairment: No study was conducted in subjects with hepatic impairment.

Age: Alzheimer's disease population generally consists of patients older than 75 years. Appropriate representation of age has not been included in the PK studies.
Subjects upto 71 years of age were enrolled in the PK studies. In cross study comparions no significant differences were seen in exposure between young (18-35 years) and older (51-69 years) subjects, but t1/2 was increased by 39% with age after a single dose of 2x 10 mg. After multiple doses of 1x10 mg BID for 18 days the subjects $\geq$ 65 years had 30% and 27% higher Cmax and AUC0-inf, respectively. 2 PK studies had a total of six subjects that were $\geq$65 years of age. Clinical relevance of these differences cannot be assertained due to the small number of subjects in the elderly group. Plasma concentrations of memantine were obtained in Phase 3 clinical trials which do not show major differences in elderly compared to younger healthy volunteers.

Gender: No apparent gender effect was observed in the pharmacokinetics of memantine.

Race: The effect of race was not evaluated. In a cross study comparison the pharmacokinetic parameters of memantine were not different between Japanese and Caucasians.

AIDS: AIDS patients had about 35% and 24% reduction in Cmax after single and multiple doses of memantine. There was a 32% and 29% reduction in AUC after single and multiple doses of memantine.

Drug-drug Interactions:
Memantine is neither a substrate nor an inhibitor of CYP isoenzymes, hence drug-drug interaction with other CYP substrates is unlikely. Memantine is eliminated via tubular secretion, therefore drugs with the same mechanism of elimination were evaluated in the drug-drug interaction studies.
Only two drug interaction studies with hydrochlorthiazide/triamterene and donepezil have been conducted so far. Ongoing drug interaction studies are with glyburide/metformin and gabapentin.

Effect of memantine on other drugs:
Memantine decreased the Cmax and AUC of hydrochlorothiazide by about 20%. Therefore a slight reduction in diuretic effect may be observed when memantine is co-administered with hydroclorothiazide/triamterene.
Memantine did not have any effect on the pharmacokinetics of other drugs studied.

Effect of other drugs on memantine pharmacokinetics:
Hydroclorothiazide/triamterene or donepezil did not influence the pharmacokinetics of memantine. No other drug-drug interaction study was conducted.

Biopharmaceutics:

- BCS Class: Memantine is highly soluble, highly permeable and rapidly dissolving drug and can be classified as BCS Class I compound.
- Bioequivalence: The Merz formulation of memantine used in the PK and clinical studies is bioequivalent to the to-be-marketed Forest formulation.
- Food Effect: Food did not affect the bioavailability of memantine
- Dissolution: The dissolution methodolgy is USP I at 100 rpm with 0.1 N HCl with NaCl at pH 1.2. A Q of − % in 30 minutes was set as the quality control specification.

APPEARS THIS WAY
ON ORIGINAL

4.0 QUESTION BASED REVIEW

4.1 GENERAL ATTRIBUTES

4.1.1 Drug/Drug Product Information:

Dosage Form/Strengths: 5, 10, 15 and 20 mg Tablets

Indication: Treatment of moderate to severe dementia of Alzheimer's type

Dosage and administration (Sponsor's Proposed):

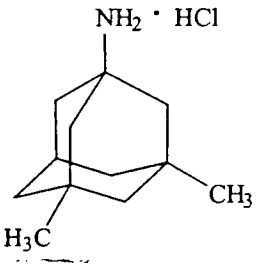
The dosage of memantine hydrochloride shown to be effective in controlled clinical trials is 10-20 mg/day.

The recommended starting dose of memantine is 5 mg once daily. The recommended target dose is 20 mg/day. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day). The minimum recommended interval between dose increases is one week.

Memantine can be taken with or without food.

Pharmacologic Class: Memantine HCl is a moderate affinity uncompetitive (open channel) NMDA receptor antagonist that binds preferentially to the NMDA receptor-operated cation channels in a use dependent and voltage dependent manner with rapid blocking/unblocking kinetics.

Chemical Name: 1-amino-3,5,-dimethyladamantane hydrochloride with the following structural formula



The molecular formula is $C_{12}H_{21}N.HCl$ and the molecular weight is

Physical Characteristics: Memantine HCl occurs as a fine white to off-white powder and is highly soluble in water, [redacted]

Mechanism of action: In vitro electrophysiological studies suggest that memantine inhibits NMDA receptor-mediated currents in a use-dependent [i.e., it blocks the receptor channel in the presence of an agonist, e.g., glutamate] and voltage-dependent manner, with rapid receptor-unblocking kinetics. Because of these attributes, memantine can selectively antagonize pathological activation of NMDA receptors without affecting the physiological functioning of the receptor. Physiological activation of NMDA receptors is known to play a critical role in synaptic plasticity processes such as cognition.

In several in vitro and in vivo studies, memantine has been shown to protect neurons from cell death due to excitotoxicity. In addition, memantine attenuates β-amyloid (Aβ)-induced hippocampal cell death (apoptosis) in rats in vivo, and protects cholinergic neurons of the rat nucleus basalis magnocellularis from NMDA-induced neurotoxicity.

Memantine has also been shown to improve learning and memory in animal studies.

Foreign marketing history: Memantine HCl was first approved in Germany on June 26, 1978 as drop and tablet dosage form for the treatment of Organic brain syndrome (nor dementia), parkinson's disease and spasticity. As of November 30th, 2002, the product has received marketing authorization in 41 countries. It is marketed under the tradename Akatinol® in 23 countries for the treatment of mild to moderate dementia syndrome. On May 21, 2002, Merz Pharmaceuticals received registration for memantine by the European Union for both drop and tablet dosage forms under the tradename Axura® for the treatment of moderately severe to severe Alzheimer's disease. For commercial reasons, memantine was voluntarily withdrawn in Hungary, Czech Republic, and Slovak Republic (approved as Akatinol®). No safety and efficacy concerns were involved in the withdrawal. [redacted]

Formulation: Quantitative formula for all the dose strengths for the Forest tablets is as follows. The tablets are compositionally proportional in that

all the ingredients increase proportionally with dose. The same blend composition is used to compress the memantine HCl tablets for the four different strength tablets, therefore the Forest Tablets increase in size with the increase of dose. Most pharmacokinetic and clinical efficacy/safety studies (Study 9202, 9403, 9408 and 9605) were conducted with the Merz formulation. In the Merz formulation the size of the tablet remained the same, only the active ingredient increased with dose and the amount of lactose changed accordingly. Clinical Study MEM-MD-02 (one of the pivotal Phase III studies) was conducted with the Forest formulation. A bioequivalence link has been established between the Merz and Forest formulations for the tablet.

Ingredients (core)	*5 mg*	*10 mg*	*15 mg*	*20 mg*
	mg/tablet	*mg/tablet*	*mg/tablet*	*mg/tablet*
MEMANTINE HCL	5.00	10.00	15.00	20.00
Lactose Monohydrate, NF				
Microcrystalline Cellulose, NF				
Colloidal Silicon Dioxide, NF				
Talc, USP				
Magnesium Stearate, NF				
Subtotal Weight (mg)				
Ingredients (Film coat)				
TAN		-	-	-
Gray	-		-	-
Purple	-	-		-
White	-	-	-	
Total Coated Tablet Weight (mg)	128.75	257.5	388.1	515.0

4.2 GENERAL CLINICAL PHARMACOLOGY

What efficacy and safety information contribute to the assessment of the clinical efficacy and safety studies?

The efficacy and safety of memantine was established in two Phase 3 pivotal randomized, double-blind, placebo-controlled multi-center trials conducted in patients with moderate to severe dementia of Alzheimer's type (DAT). Patients enrolled had a Mini-Mental State Examination Score (MMSE) of 3-14 and diagnosis of Alzheimer's disease according to NINCDS-ADRDA criteria.

- In Study 9605, a total of 252 patients were randomized to a 28 week study. Patients assigned to memantine treatment received a starting dose of 5 mg once daily and were titrated over a 3-week period to a dose of 20 mg/day

(given as 10 mg twice a day). This study had an open label extension up to 1 year.

- In Study MEM-MD-02, a total of 404 patients were randomized to a 24 week study. Randomized patients had received donepezil (Aricept®) therapy for at least 6 months and at a stable dose (5-10 mg) for the last 3 months prior to randomization and continued to receive donepezil for the duration of the therapy. Patients assigned memantine treatment received a starting dose of 5 mg once daily and were titrated over a 4-week period to a dose of 20 mg/day (given as 10 mg twice a day). This was followed by an optional 28 week memantine treatment extension period.

Other supportive studies were:

- In Study 9403, a total of 166 patients were randomized to a 12 week study. Patients assigned memantine treatment received a starting dose of 5 mg once daily for 1 week and 10 mg once daily thereafter. This study was conducted in patients with moderate to severe dementia of the Alzheimer's type.
- In Study 9202, a total of 581 patients were randomized to a 28 week Study. Patients assigned memantine treatment received a starting dose of 5 mg once daily and were titrated over a 3-week period to a dose of 20 mg/day (given as 10 mg twice a day).
- In Study 9408, a total of 321 patients were randomized to a 28 week Study. Patients assigned memantine treatment received a starting dose of 5 mg once daily and were titrated over a 3-week period to a dose of 20 mg/day (given as 10 mg twice a day).

  Studies 9202 and 9408 were conducted in patients with mild to moderate vascular dementia.

Safety:

Some of the common side effects were agitation, cerebrovascular disorder, confusion, pneumonia, fall, inflicted injury, nausea, depression, somnolence, dizziness. Dizziness appeared to be dose related with majority of cases occuring in the 40 mg/day dose group. Other side effects were constipation, coughing, diarrhea, hypertension, anxiety, hallucination, pain etc. The potentially clinically significant (PCS) vital sign was for high systolic blood pressure. The most frequent PCS laboratory values were high serum potassium, cholesterol, urea nitrogen and low hemoglobin.

Effect of memantine on QTc prolongation:

There were no clinically important mean changes in ECG interval values or ECG determined heart rate from baseline to end of study in either the memantine or placebo patients.

In the double-blind, placebo-controlled dementia studies, 19% of placebo and 21% of memantine patients who had a normal ECG at baseline had an abnormal result at end of

study. In the double-blind, placebo-controlled neuropathy studies, 15% of placebo and 23% of memantine patients who had a normal ECG at baseline had an abnormal result at end of study.

The incidence of PCS interval values was infrequent and similar between the memantine and placebo treatment groups.

What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

The endpoint measures to assess efficacy in terms of functional, cognitive and global outcomes were:

Study 9605 and MEM-MD-02:

- For Functional Assessment: Modified Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL): consists of a 19 item subset of questions. A total of 54 points signifies optimal performance.
- For Cognition Assessment: Severe Impairment Battery (SIB): This test consists of 51 items with scores ranging from 0-100, with 100 being the best result and low score suggesting more severe impairment.
- For Global Status Assessment: Clinical Interview Based Impression of Change (CIBIC-Plus): ratings done on a 7-point ordinal scale with 1=marked improvement.

Study 9403:

- For Functional Assessment: Behavioral Rating Scale for Geriatric Patients (BGP). Care Dependency Scale: This scale consisted of 23 items assessing observable behavior each of which could be rated as 0, 1 or 2 by the nursing staff. A BGP care dependency score could range from 0-46, with higher values denoting greater impairment.
- For Cognition Assessment: BGP cognitive subscale: This subscale consists of 5 items, with scores ranging from 0-10, with higher values denoting greater impairment.
- For Global Status Assessment: Clinical Global Impression of Change (CGI-C): ratings based on a 7-point symmetrical categorical change measure with 1=very much improved

Study 9202 and 9408:

- For Cognition Assessment: Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog): This is a 11 item scale to assess severity of cognitive impairment, scores can range from 0-70, with higher scores indicating greater severity of impairment.
- For Global Status Assessment: Clinical Global Impression of Change (CGI-C) for Study 9202: ratings based on a 7-point symmetrical categorical change measure with 1=very much improved.

CIBIC-plus for Study 9408.

Hence, different primary outcome measures were used in different studies and can be summarized in the following Table, with 'P' denoting primary endpoint and 'S' denoting secondary endpoint. There were several secondary measures all of which are not listed here:

Study	Functional	Cognitive	Global
9605	ADCS-ADL (P)	SIB (S)	CIBIC-Plus (P)
MD-02	ADCS-ADL (P)	SIB (P)	CIBIC-Plus (S)
9403	BGP-Care Dependency (P)	BGP-cognitive (post hoc P)	CGI-C (P)
9202	-	ADAS-cog (P)	CGI-C (P)
9408	-	ADAS-cog (P)	CIBIC-Plus (P)

What are the characteristics of exposure/response relationships in patients for efficacy or safety? Can disparate efficacy measurements or safety information be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients?

No exposure response relationship was observed for either efficacy or safety, hence, the disparity in the efficacy and safety data cannot be attributed to any intrinsic or extrinsic factors that alter drug exposure response relationships in patients.

For Efficacy:
Plasma concentrations of memantine were determined in samples obtained at the final visit of one Study 9605 in 108 memantine treated patients. An analysis to assess the relationship between plasma levels of memantine and the change from baseline in cognitive abilities was conducted using the endpoint (last observation carried forward - LOCF) and Week 28 (observed case-OC) data for the Severe Impairment Battery (SIB) endpoint.

Patients treated with memantine were grouped according to their memantine plasma concentration at study endpoint into four categories given in the foilowing Table based on plasma concentration range.

	Placebo	Memantine			
		≤70 ng/mL	71-100 ng/ml	101-130 ng/ml	> 130 ng/ml
Endpoint (LOCF)	-10.22	-4.00	-4.25	-4.44	-4.66
Week 28 (OC)	-10.16	-5.20	-3.92	-4.96	-4.35

In the LOCF data, numerically the least mean worsening in cognition was observed in the small group of patients (N=7) making up the ≤70 ng/mL group, who displayed a mean change of -4.0 points. The greatest mean change (-4.66 points) was seen in the group of patients with the highest plasma levels (> 130 ng/mL). In contrast, in the OC data, the

smallest mean decline was seen in the 71 to 100 ng/mL group and the largest mean change was observed in the ≤70 ng/mL group. These results fail to provide evidence of a consistent relationship between plasma concentrations of memantine and the response to memantine treatment in patients with moderate to severe DAT.

For Safety:
No relationship was observed between adverse events and exposure. Dizziness was the only adverse event that appeared to be dose related with majority of cases occuring in the 40 mg/day dose group (32.7%). The other adverse events with incidence rates ≥5% in the 40 mg dose group were headache (11.4%), fatigue (7.3%), paresthesia (6.8%), upper respiratory tract infection (6.4%), back pain (5.9%) and somnolence (5.0%). The incidence of treatment emergent adverse events (TEAE) was higher in the 40 mg dose group as compared to the ≤20 mg dose group. Overall incidence of TEAE was similar between the ≤20 mg dose group and placebo patients. There was no dose related effect on syncope or falls. Overall no dose relationships were noted with the serious adverse events as well. The maximum daily dosing proposed is 20 mg/day.

Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response?

The sponsor has not conducted any dose-response analysis to support the dosage recommendation of memantine. Dosing recommendations are based on previous clinical experience from Europe since 1978. Initial studies conducted in 1984 suggested that there was an increase in drop out rates when the dose was rapidly increased in steps of 20 mg/day to 60 mg/day. In most earlier studies the starting dose was 10 mg/day. It was decided that a slower upward titration would improve tolerability. This could be done in two ways: by reducing incremental dose or by prolonging the time interval between changing the dose. On this basis it was decided by the sponsor to initiate therapy on 5 mg and titrate upwards on weekly intervals by steps of 5 mg. The dosing recommendations for this NDA were based on the vast information available from several years of clinical experience in Europe.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Three main assay methodologies were used for the determination of memantine in plasma and urine. Even though the validation for the [redacted] methodology did not fully meet the bioanalytical method validation guidance recommendations, the data supported the accuracy, precision and selectivity to some extent. The validation was conducted according to the general ICH guidelines. The sponsor provided additional data [redacted] to support the various components of the validation methodology. Numerous limits of quantitation were used in

different studies using the same methodology. In most cases these LLOQs were within the calibration range for the standard curve. Some studies lacked quality control data, but standard curve for each day was provided. Though the assay validation was not conducted as per the current FDA guidelines on Bioanalytical Validation, these non pivotal studies were accepted based on the following reasons: (a) no apparent drift was observed during the analytical runs conducted with studies that had quality control data, (b) pharmacokinetic parameters obtained from the studies with no QC data were very similar to those from other studies with adequate QC at same doses, (c) the pharmacokinetic parameters obtained from studies that utilized — were similar to the studies that utilized — for evaluating the memantine concentrations at similar doses.

The main methods are given below. For validation parameters see section 4.6.

Method 1: — method was utilized in the determination of memantine in the plasma and the urine for studies conducted between 1990-1995. In this method the LLOQ for memantine was —g/ml in plasma and — ng/ml in urine

Method 2: In 1996, A method utilizing — after derivatization with MBTFA was utilized in the determination of memantine. In this method the LLOQ for memantine was — ng/ml in plasma and — ng/ml in urine.

Method 3: In 2001, — methodology was developed for the determination of memantine in plasma. The LLOQ for memantine was — ng/ml in plasma.

Some other methods were used which were slight modifications of these methods and have been given in section 4.6.

What are the general ADME (absorption, distribution, metabolism and elimination) characteristics of memantine?

The key points of the ADME characteristics of memantine are summarized below:

Absorption:

- Memantine is highly absorbed. An accurate estimate of absolute bioavailability is questionable at this time. High variability was seen in the results of the study. It appears that the absolute bioavailability decreases with the increase in dose (149% at the 10 mg dose and 97% at the 40 mg dose). The reasons for this could be postulated as: some degree of non linearity at the lower doses or uncontrolled diet during the study (clearance reduction under alkaline urine conditions) or an inaccurate dose of the IV.

- The Tmax ranged from — hours. The Tmax in most studies was between 5-7 hours with 2 x 10 mg memantine given at one time. The Tmax appeared to be slightly higher (—), when a 20 mg dose was given as divided doses of 10 mg each.
- The transport of memantine did not appear to be mediated via Pgp or multi-resistant gene related protein (MRP).

Distribution:

- In vitro protein-binding of memantine ranged from 41.9-45.3% over the concentration range of 0.5-10 μM.
- Mean Vd/F following a single dose is 846.7 ± 123.3 L.
- The volume of distribution following intravenous doses of 20, 30 and 40 mg memantine was approximately 9-11 L/kg suggesting extensive distribution of memantine in tissues.

Metabolism:

- An —— analysis on urine of one subject showed that memantine is poorly metabolized in man forming small quantities of oxidative metabolites. Memantine, the major radiolabeled component accounted for approximately 68% of the characterized material. Two other components amounted to approximately 15% and 17% of the radioactivity.
- Metabolic profiling of memantine showed that the proportion of intact memantine excreted in urine increased over the first 12 hour post dose, rising from 30-67% of the radioactivity in the 0-6 h samples to 42-82% in the 6-12 h samples. The amount of radioactivity associated with the metabolites decreased with time, falling from 19-26% in the 0-6 h samples to <15% in the 216-240 h samples.
- The predominant route of memantine metabolism was via hydroxylation to form 1-amino-3- hydroxymethyl-5-methyladamantane (MRZ 2/373, 11-hydroxy memantine), 1-amino-3,5-dimethyl-7- hydroxyadamantane (MRZ 2/544, 7-hydroxy memantine), and MRZ 2/374 (6-hydroxy memantine). Other routes of metabolism are N-oxidation and conjugation.
- These metabolites did not have any NMDA antagonist activity.
- CYP 450's isoenzymes do not play a role in the metabolism of memantine.
- Memantine is a low extraction ratio drug.

Elimination:

- Mass balance study suggests renal as the major route of elimination (83% of total radioactivity in urine) mainly as unchanged drug but also due to metabolites to some extent. The extent of renal elimination of intact drug is not very clear with the studies submitted due to conflicting results from 3 studies. One study showed that about 57% -82% of ^{14}C memantine was excreted as intact drug by renal elimination. The other two studies showed that the renal clearance of memantine amounted to about 90% and 50%, respectively of the total clearance, suggesting the remaining to be non renal clearance. A multiple dose study (Study 610/6) suggested that 71-85% of the dose is

excreted non renally after multiple dose. These values were much higher than the other studies.

The recovery of radioactivity in the urine and feces is shown in the following Table.

Table: Recovery of Radioactivity in Urine and Feces (%Dose) Following a Single Oral Dose of ^{14}C-Memantine Under Steady-State Conditions in Healthy Subjects

Tissue	*Subject*						*Mean ± SD*
	1	*2*	*3*	*4*	*5*	*6*	
Feces	1.344	0.341	0.294	0.274	0.540	0.440	0.539 ± 0.407
Urine	90.10	91.82	74.02	90.33	89.19	63.53	83.16 ± 11.66
Total	91.44	92.16	74.31	90.60	89.73	63.97	83.70 ± 11.77

- The majority of the radioactivity was excreted in urine, representing a mean (SD) of 83.16±11.77% of the administered radioactive dose within a 480 h period.
- Minimal radioactivity was detected in feces which averaged 0.54%.
- Recovery in sweat was low.
- The mean elimination t1/2 ranged between 57-95 hours across studies.
- The elimination t1/2 was and did not change with the increase in dose suggesting dose independent elimination.
- Renal elimination is in part due to active tubular secretion and also due to pH dependent tubular reabsorption.
- The renal clearance accounted for 90% of total memantine clearance under physiological conditions and 92% under acidic conditions. Renal clearance of memantine under alkaline conditions was 60% and 67% of total clearance at low and high urinary flow respectively.
- Clearance under normal physiological conditions: The total clearance ranged on an average from 127 to 182 ml/min and renal clearance of memantine on an average ranged from 150-164 ml/min across studies. These clearances exceed clearance by glomerular filtration indicating a substantial contribution of tubular secretion.
- Clearance under alkaline conditions: The total and renal clearance of memantine was reduced (78% and 87% respectively) under alkaline urine conditions. The decreased renal clearance under alkaline conditions may be due to increased tubular reabsorption as the pH approaches the pKa of memantine (— — , and the molecule becomes unionized. Therefore, alterations of urine pH towards alkaline conditions may lead to an accumulation of the drug with a possible increase in side effects. Urine pH is altered by diet, drugs and clinical state of the patient (eg. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.
- Clearance under acidic conditions: Acidic urine conditions caused an increase in the memantine total and renal clearance up to 30 % and 34% respectively.
- Changes in urinary flow did not have clinically relevant influence on renal excretion of memantine.

What are the basic pharmacokinetic parameters of memantine after single and multiple doses?

Single Dose:

The pharmacokinetics of memantine have been evaluated in 11 single dose studies that have been reviewed. In most studies a single dose of 2 x 10 mg was evaluated. In one study (MEM-PK-04), a single dose of 2 x 10 mg memantine was administered in a divided dose, with 10 mg being given twice a day at 0800 and 1200 hours. The proposed dosing also recommends doses being given in divided doses (see page 9). The pharmacokinetics of 1x10 mg memantine were studied in the donepezil drug-drug interaction study. The pharmacokinetic parameters were similar across studies. Pharmacokinetic parameters from few studies conducted appropriately with adequate assay validations are summarized below:

Table: Pharmacokinetic Parameters (Mean ± SD) of Memantine Following a Single Dose of 1x 10 and 2 x 10 mg IR Tablet Healthy Young Subjects

Parameter	*1 x 10 mg IR tablet (n=19)* (Studt MEM-PK-07)	*2 x 10 mg IR Tablet (n = 12)* (Study 9604)	*2 x 10 mg (given in divided dose 4h apart) IR Tablet (n = 20)* (Study MEM-PK-04)	*2 x 10 mg IR Tablet (n = 23)* (Study MEM-PK-01)	*2 x 10 mg IR Tablet (n = 6)* (Study 1E1801)
C_{max} (ng/mL)	12.8 ± 2.4	23.8 ± 5.3	24.92 ± 4.82	24.7 ± 4.4	28.98 ± 3.65
T_{max} (h)	6.5 ± 2.1	3.3 ± 1.7	8.2 ± 2.0	5.0 ± 2.0	6.0 ± 3.8
AUC_{0-t} (ng h/mL)	958 ± 147.2	1568.7 ± 300.7	1898.2 ± 453.0	1840.4 ± 435.9	2362.2 ± 476.4
$AUC_{0-\infty}$ (ng h/mL)	1124.5 ± 211.3	1716.2 ± 358.0	1969.0 ± 455.8	1898.7 ± 444.3	2497.6 ± 482.8
$T_{1/2}$ (h)	70.9 ± 24.1	63.7 ± 12.6	57.4 ± 14.2	55.9 ± 10.7	71.3 ± 12.6

These results show that the single dose pharmacokinetics of 2 x 10 mg memantine are similar across studies. The exposure from 2 x 10 mg memantine appears to be approximately proportional to 1 x 10 mg memantine. The Tmax ranged from 3.3-7 hours. The Tmax in most studies was between 5-7 hours with 2 x 10 mg memantine given at a one time. The Tmax appeared to be slightly higher (8.2 hours), when a 20 mg doses was as divided doses of 10 mg each. The Cmax, AUC and T1/2 were similar in the studies where a 20 mg dose was administered as a single dose or as divided doses given 10 mg BID.

Multiple Dose:

The pharmacokinetics of memantine after multiple doses were evaluated in 7 studies including drug interaction studies and special population studies that have been reviewed.

The following Table lists studies that give multiple dosing information and the dosing regimen used in these studies are given below:

Study	Dosing Regimen
Study 9704	Day 4-8: 1 x 10 mg IR tablets QD Day 9-27: 1 x 10 mg IR tablets BID (20 mg/day) Day 28: 2 x 10 mg IR tablets SD
Study 9402 (supportive)	Days 1-5: 1 x 10 mg tablets QD Days 6-26: 1 x 10 mg tablets BID (20 mg/day) Day 27: 2 x 10 mg tablet SD
Study 9702 (HCTZ/TA DDI) Period 2 of the study where memantine was administered alone)	Days 5-7: 5 mg tablets QD Days 8-11: 1x 10 mg tablets QD Day 12-25: 2 x 10 mg tablets QD
Study HUK 610/6	Parallel groups: ½ x 10 mg tid (15 mg/day for 12 days) 1 x 10 mg tid (30 mg/day for 12 days) 2 x 10 mg tid (60 mg/day for 12 days)

Only results from Study 9702 and 9402 will be discussed in this section, because in Study HUH 610/6 doses were given TID and were above the recommended therapeutic doses. Study 9402 should only be used as supportive information because of the lack of quality control data, although the pharmacokinetic parameters of memantine are similar to that in Study 9704.

The pharmacokinetic parameters after multiple 20 mg doses of memantine to healthy elderly subjects (ages 50-71 years), is given in the following Table:

Table: Pharmacokinetic Parameters (Mean ± SD) of Memantine Following Multiple 20 mg Doses of an Immediate Release Formulation in Healthy Elderly Subjects

Parameter	*1 x 10 mg BID (n = 24) (Study 9704)*	*1 x 10 mg BID (n = 24) (Study 9402) (supportive)*	*2 x 10 mg QD (n = 20) (Study 9702)*
C_{max} (ng/mL)	85.83 ± 22.87	91.3 ± 18.7	100.7 ± 21.3
T_{max} (h)	5.15 ± 2.93	4.5 ± 1.5	4.45 ± 2.57
AUC_{0-24} (ng h/mL)	1803 ± 492	1848.5 ± 408.7	2057 ± 479
AUC_{0-t} (ng h/mL)	-	8162.9 ± 3655.9	-
$AUC_{0-\infty}$ (ng h/mL)	-	8836.9 ± 4048.5	-
C_{min} (ng/mL)	65.66 ± 16.67	63.0 ± 15.8	69.5 ± 17.8
C_{av} (ng/mL)	-	77.0 ± 17.0	85.7 ± 20.0
%Fluctuation	34.9 ± 7.8	37.51 ± 9.19	37.3 ± 5.7
T_{Cav} (h)	12.66 ± 1.31	11.53 ± 1.14	-
$T_{1/2}$ (h)	-	72.26 ± 19.55	-

- Based on the multiple dose studies, steady state appears to reached between 13-16 days, which is consistent with the half-life of memantine.

Do the pharmacokinetic parameters change with time following chronic dosing?

Single doses of memantine predict multiple dose pharmacokinetics of memantine. There will be significant accumulation upon multiple dosing. An accumulation factor of approximately 10 can be predicted based on the t1/2 of 60-80 hours. Studies 9402 and 9702 could not estimate accumulation as plasma samples were not taken after a single dose on Day 1. Only steady state pharmacokinetics were assessed in these studies. Study MEM 9601 supports the prediction of the accumulation factor based on linear pharmacokinetics. In this study 3 subjects gave a mean AUC0-12 of 138.85 ng.hr/ml after a single dose of 1x 10 memantine. After 2x 10 mg (given as divided doses) for 5 weeks the mean AUC0-12 was 1226 ng.hr/ml. This suggests an accumulation factor of 10 on multiple dosing. Study HUK 610/6 though conducted with a TID regimen showed a Cmax accumulation ratio of 15. Accumulation based on AUC could not be estimated from this study. The accumulation factor predicted for TID dosing is approximately 15 suggesting single dose pharmacokinetics predicts multiple dose pharmacokinetics of memantine.

How do the pharmacokinetics of the drug in healthy volunteers compare to that in patients?

The pharmacokinetics of memantine in the patients with dementia of vascular type were assessed in the following Phase 2 and 3 studies:

Study number	Study Design	Patient Population	Study Duration	Dosing	Blood Sampling
Study 9403	Multi-center, Randomized double-blind Placebo controlled	Moderate to severe dementia of alzheimer's type or vascular dementia	12 weeks	Week 1: 5 mg QD Week 2+: 10 mg QD	Week 4 and 12 Before dosing Timing for all patients not available
Study 9605	Multi-center, Randomized double-blind Placebo controlled Randomized period followed by a 24 week open label	Moderate to severe alzheimer's disease	28 weeks	Week 1: 5 mg QD Week 2: 10 mg QD Week 3: 10 mg at breakfast and 5 mg at lunch Week 4: 10 mg at breakfast and 10 mg at lunch	Week 12 and 28 Timing not recorded

Study 9408 Phase 3	Multi-center, Randomized double-blind Placebo controlled Randomized period followed by an open label	Mild to moderate vascular dementia	28 weeks	Week 1: 5 mg QD Week 2: 10 mg QD Week 3: 10 mg at breakfast and 5 mg at lunch Week 4: 10 mg at breakfast and 10 mg at lunch	Week 12 and 28 Timing not recorded
Study 9202 Phase 3	Multi-center, Randomized double-blind Placebo controlled Randomized period followed by a 24 week open label	Mild to moderate vascular dementia	28 weeks	Week 1: 5 mg QD Week 2: 10 mg QD Week 3: 10 mg at breakfast and 5 mg at lunch Week 4: 10 mg at breakfast and 10 mg at lunch	Week 12 and 28 Timing not recorded

The plasma concentrations of memantine in the sampling weeks at steady state are shown in the following Table:

	Week 4	Week 12	Week 28
	Mean (%CV) memantine plasma concentration (ng/ml)		
Study 9403	50.8 (39.8) Range= — N=78	50.2 (45) Range= — N=78	-
Study 9605	-	118.6 (33.4) Range= — N=106	103.9 (40.9) Range= — N=93
Study 9408	-	121.8 (34.9) Range= — N=116	108.5 (50.5) Range= — N=115
Study 9202	-	133.1 (36.6) Range= — N=219	138.4 (40.7) Range= — N=115

LLOQ —ıg/ml

This Table shows that:

- Plasma concentrations at the two sampling weeks are similar showing that steady state is reached by Week 4 in these studies.
- Plasma concentrations obtained from identical dosing regimen studies are similar. In Study 9403 patients received only up to 10 mg/day, hence, the levels are half of that

obtained from the other 3 studies where the patients received up to 20 mg/day of memantine.

The only study in which the timing of the sampling was known from some subjects shows the following steady state plasma concentrations of memantine at weeks 4 and 12.

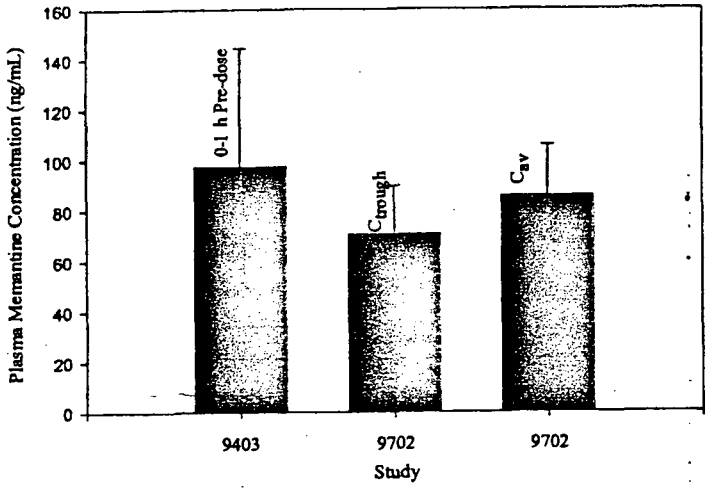
	>1 h Predose (n=3)	0-1 h Predose (n=26)	>0-1 h Predose (n=35)
Mean (%CV)	50.8 (10)	48.7 (48.6)	56.1 (38)
Range			

Comparison of plasma concentrations in patients to that in healthy volunteers:

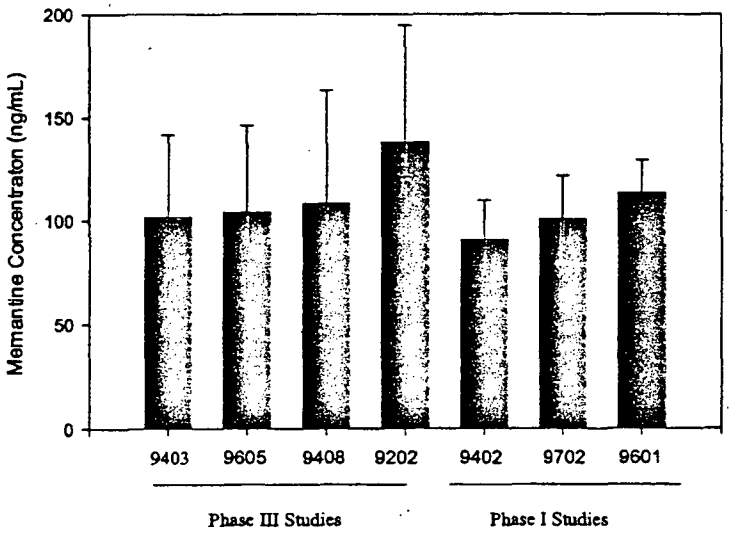
The pharmacokinetics of memantine in patients are compared to that in healthy volunteers from 3 multiple-dose studies. The mean plasma concentrations from memantine from these studies are given in the following Table:

Study	Dosing Regimen	Dose on Day of PK Sampling	Cmax (ng/ml)	Ctrough (ng/ml)	Cav (ng/ml)
Study 9702 (n=20)	20 mg QD	20 mg	100.7 ± 21.3	70.5 ±19.0	85.7 ± 20.0
Study 9402 (n=24)	10 mg BID (20 mg/day)	20 mg	91.3 ± 18.7	64.8 ± 17.7	77.0 ± 17.0
MEM 9601, NTI0015 (n=3)	10 mg BID (20 mg/day)	10 mg	113.7 ± 15.5	95.7 ± 18.5	102.2 ± 13.7

Graphical comparisons of the studies is shown in the following figures. Comparison of the predose concentrations (dose adjusted) from Study 9403 (only study where the timing of the sampling was known) to Study 9702 in healthy volunteers is shown in the following Figure. Since memantine has a long t1/2 it can been assumed that the peak-trough fluctuation will be very less, hence we can assume that the plasma concentrations in patients will approximate the average steady state concentrations.



Comparisons to other Phase I studies is given below:



Although a robust comparison cannot be made between patients and healthy volunteers, these figures suggest that the memantine average plasma concentrations in these population may be comparable, however range of the steady state concentrations were higher in the Alzheimer's patient population.

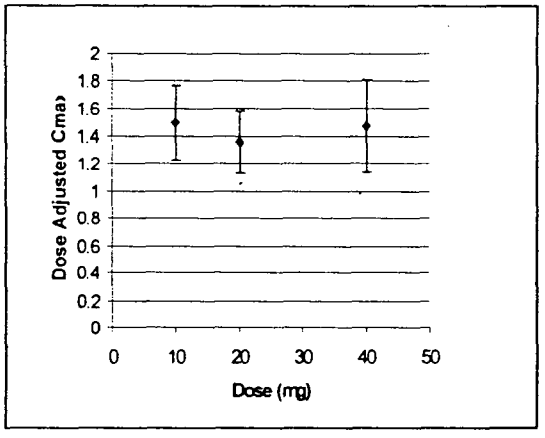
Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose proportionality has been assessed in Study 610/4 (crossover design) and Study 1E1801 (parallel design).

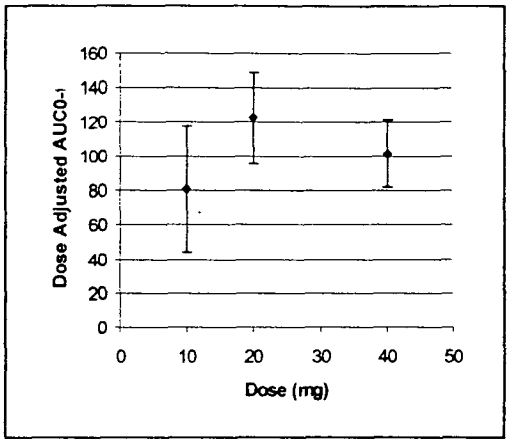
A power analysis to assess dose proportionalilty for Study 610/4 and 1E1801 showed that the pharmacokinetics were approximately dose proportional (if estimate close to 1 and the 95% CI includes 1 or very close to it).

Study	Doses Studied	Parameter	Estimate	95% CI
610/4 (crossover)	10, 20 and 40 mg	AUC0-t	1.21	0.89-1.35
		Cmax	0.985	0.85-1.12
1E1801 (parallel)	5, 10 , 20 and 40 mg	AUC0-inf	1.105	1.06-1.25
		Cmax	1.059	1.01-1.25

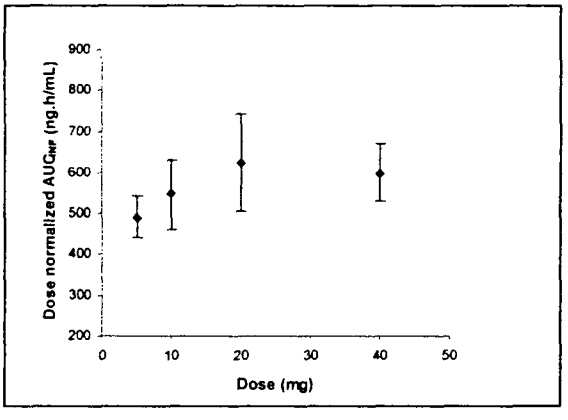
Graphically these can be shown as below:



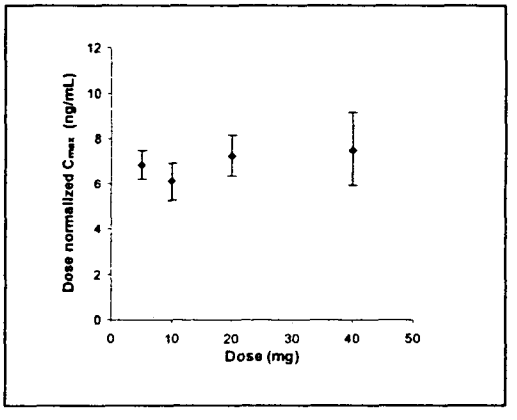
Study 610/4



Study 610/4



Study 1E1801



Study 1E1801

4.3 INTRINSIC FACTORS

4.3.1 Effect of Renal Impairment:

A study to assess the effect of renal impairment has been conducted, but the quality control samples were not provided with the study. Standard curve figures were given but accuracy and precision for the standard curves were not reported. Upon request, the sponsor provided newly generated excel spreadsheet with back calculated concentration in plasma standards and showed tight accuracy and precision between these standards. The LLOQ was lower (than the validated range (5-200 ng/ml) using the same assay methodology. Hence, results cannot be concluded to be reliable at this time.

The results although not reliable, showed that:

- A single 20 mg dose of memantine caused reduction in total clearance 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.
- Another study in all categories of renal impairment is ongoing and the sponsor intends to submit the report by mid 2004. Based on these results a dose reduction needs to be considered in patients with moderate renal impairment. However, it would be more appropriate to add the quantitative information to the label when the results of the new study being conducted are available. At this point a general statement regarding dose adjustment in patients with renal impairment will be included.

4.3.2 Effect of Hepatic Impairment:

About 57 to 82% of memantine is eliminated intact in the urine based on a radiolabeled study in 6 subjects. This shows that about 18-43% of the memantine is eliminated through the metabolic route. A pharmacokinetic study has not been conducted in patients with hepatic impairment. Metabolic profiling conducted in one subject showed that memantine accounted for about 68% of the characterized material and two other components accounted for 15% and 17% of the radioactivity. In vitro studies show that CYP isoenzymes are not involved in the metabolism of memantine. The sponsor claims that memantine is minimally metabolized, hence a study in hepatic impaired subjects is not warranted. The Phase III clinical studies did not stratify the patients based on the extent of hepatic impairment. Based on up to 43% elimination via metabolic route, hepatic impairment study especially in patients with moderate hepatic impairment should be conducted.

4.3.3 Effect of age:

After Single Dose:
Effect of age has been evaluated in subjects in the age range of 51-69 years (mean 57 years) after a single dose of 2 x 10 mg memantine in Study 9506 compared to younger subjects in the age range 18-35 from study MEM-PK-01. Most Alzheimer's disease subjects are ≥ 65 years. The mean age in the clinical efficacy trials was around 75 years. A cross study comparison in the young and older subjects is given in the Table below. Dividing the population at 65 years did not make sense with this data set as there were only 2 subjects that were ≥ 65 years.

Table: Pharmacokinetic Parameters (Mean ± SD) of Memantine Following a Single Dose of 2 x 10 mg Immediate Release Tablet in Healthy Young and Elderly Subjects

Parameter	*2 x 10 mg IR Tablets*	
	Ages 51-69 (n=22) (Study 9506)	*Ages 18-35 (n=23) (Study MEM-PK-01)*
C_{max} (ng/mL)	23.80 ± 6.10	24.4 ± 4.4
T_{max} (h)	6.55 ± 7.99	5.6 ± 0.8
AUC_{0-t} (ng h/mL)	1998 ± 514	1878.5 ± 468.1
$AUC_{0-\infty}$ (ng h/mL)	2174 ± 564	1939.7 ± 472.1

$T_{1/2}$ (h)	77.79 ± 20.74	55.6 ± 10.3
CL/F (L/h)	9.82 ± 2.57	9.06 ± 2.16

- Based this cross study comparison, there do not appear to be any significant age related differences in the AUC0-t, AUC0-∞ and Cmax in the age range studied (18-69). There was a 6% ↑ in AUC0-t, 12% ↑AUC0-∞ in the older subjects (51-69 years here) which is within the varaibility in the pharmacokinetics of memantine. However, clinically relevant elderly population has not been evaluated in this study. There were only 6 subjects that were older than 60 years and 2 subjects older than 65 years in this study, which is not representative of an elderly population. These two subjects did not have pharmacokonetic parameters that were different from the rest of the population. No statistical evaluation was done as the number of subjects were very few and the percent change seems minimal.
- T1/2 increased (39%) with the increase in age, which is consistent with the decreasing renal function with increasing age. Since the AUC and Cmax were not significantly affected a dosage adjustment may not be necessary. The clinical trials had some pharmacokinetic data which has been described on page 24.

After Multiple Dose:
Effect of age after multiple dosing is evaluated from Study 9704 in subjects < 65 years and ≥ 65 years.

Table: **Pharmacokinetic Parameters (Mean ± SD) of Memantine Following Multiple 20 mg Doses of Immediate Release Tablets in Healthy Subjects**		
	2 x 10 mg IR Tablet BID	
Parameter	*<65 years*	*≥ 65 years*
	(n=19)	*(n = 4)*
C_{max} (ng/mL)	81.64 ± 21.04	106.8 ± 22.39
T_{max} (h)	5.22 ± 2.95	4.8 ± 3.25
$AUC_{0-\infty}$ (ng h/mL)	1723 ± 479	2201 ± 380

- The sponsor has not adequately addressed the effect of age in sufficient number of subjects in traditional pharmacokinetic studies. The Cmax and AUC0-∞ were 30% and 27% higher, respectively in the subjects ≥ 65 years of age after multiple doses of 10 mg BID. No statistical comparisons were done as there were only 4 subjects in the older age group. The clinical relevance of this difference cannot be asertained due to the few number of subjects.
- However, pharmacokinetic data from clinical trials in elderly patients is reasonable and does not indicate a major age effect (in elderly).

4.4.4 Effect of Gender:

The effect of gender from the following studies is given in the following Table:

Single Dose:

Table: Pharmacokinetic Parameters (Mean ± SD) of Memantine Following a Single Dose of 2 x 10 mg Immediate Release Tablet in Males and Females				
Parameter	*2 x 10 mg IR Tablets*			
	Study MEM-PK-04		*Study 9605*	
	Males (n=11)	*Females (n=9)*	*Males (n=12)*	*Females (n=10)*
Wt Adjusted ^{C}max (ng/mL)	24.64 ± 3.59	24.34 ±2.38	21.69 ± 4.05	22.09 ± 4.45
^{T}max (h)	7.4 ± 1.4	9.2 ± 2.2	7.00 ± 9.37	6.00 ± 6.41
Wt Adjusted ^{AUC}0-t (ng h/mL)	1744.4 ± 294.7	1970.6 ± 341.9	1928 ± 421	2082 ± 621
Wt Adjusted ^{AUC}0-∞ (ng h/mL)	1855.6 ± 285.7	2034.6 ± 361.9	2126 ± 512	2130 ± 374
^{T}1/2 (h)	53.4 ± 13.1	62.0 ± 14.4	82.21 ± 21.96	70.50 ± 18.89
CL/F (L/h)	-	-	9.94 ± 2.45	9.68 ± 2.82

- After adjusting for differences in body weight between male and female subjects, there were no significant differences in the pharmacokinetics of memantine in males and females as shown in the Table above with weight adjusted parameters.
- In Study MEM-PK-04, the female subjects had a 34% higher mean AUC$_{0-\infty}$ value and a 22% higher mean Cmax value than male subjects. The mean t1/2 was 15% longer in the females than in males. These differences in AUC were reduced to 9-13% after body weight adjustment ($p>0.17$ for all parameters).
- In study 9605, the female subjects had a 5% higher mean AUC$_{0-\infty}$ value and a 21% higher mean Cmax value than male subjects. Mean T1/2 value was shorter in female subjects as compared to male subjects by 14%. After adjusting for body weight there was no difference between the males and females for these parameters.

Multiple Dose:

Following multiple doses of 2x10 mg BID for 18 days, the effect of gender can be shown in the following Table:

Table: Pharmacokinetic Parameters (Mean ± SD) of Memantine Following Multiple 20 mg Doses of Immediate Release Tablets in Healthy Elderly Male and Female Subjects		
	2 x 10 mg IR Tablet	
Parameter	*Males (n = 18)*	*Females (n = 6)*
^{C}max (ng/mL)	76.73 ± 15.73	113.13 ±1 9.30
Wt Adjusted Cmax	87.96 ± 17.63	104.02 ± 18.53
^{T}max (h)	5.15 ± 3.21	5.17 ± 2.14
^{AUC}0-∞ (ng h/mL)	1620 ± 373	2352 ± 397
Wt Adjusted AUC0-∞	1856 ± 418	2164 ± 390
PTF	0.338 ± 0.080	0.383 ± 0.070
^{T}Cav (h)	12.79 ± 1.26	12.25 ± 1.48

A^e0-24 (mg)	8.63 ± 2.64	9.29 ± 1.94

- Mean Cmax and AUC0-24 values were higher in female than in male subjects by 47% and 45%, respectively, following administration of the IR formulation. Statistical evaluation showed that weight, but not gender, had a significant effect on AUC0-24 and Cmax. After accounting for weight differences, Cmax and AUC0-24 values were higher in female subjects by 18% and 17%, respectively but these differences were not statistically significant. If the drug has significant side effects, weight adjusted dosing (mg/kg) would be beneficial.

4.4.5 Effect of Race:

Effect of race has not been evaluated in pharmacokinetic studies. However a study conducted in the Japanese adult subjects did not show any difference in the pharmacokinetic parameters from those obtained in Caucasians.

4.4.6 Effect of AIDS:

After Single dose:
The pharmacokinetic parameters of memantine following a single 10 mg dose using memantine capsules in healthy subjects and AIDS patients are summarized in the following Table.

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)*
Cmax (ng/mL)	15.6 ± 1.15	10.2 ± 2.31
Cmax (ng/mL) Wt Adjusted	14.8 ± 1.3	11.7 ± 3.4
Tmax (h)	6.19 ± 1.19	6.00 ± 2.62
AUC0-24 (ng h/mL)	289 ± 25.3	191 ± 36.8
AUC0-∞ (ng h/mL)	1413 ± 270	969 ± 237
AUC0-∞ (ng h/mL) Wt Adjusted	1342 ± 263	1114 ± 330
T1/2 (h)	68.7 ± 14.3	63.7 ± 12.5
CL/F (L/h)	6.06 ± 1.11	8.97 ± 1.94
Vd/F (L)	584 ± 61.1	798 ± 109
CL/Wt (L/h/kg)	0.091 ± 0.013	0.114 ± 0.029
Vd/wt (L/Kg)	8.79 ± 0.612	10.12 ± 1.89

- Mean Cmax and AUC0-∞ values were reduced in AIDS patients by 35% and 32%, respectively relative to the values in healthy subjects.

- 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.

After Multiple Dose:

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:
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 Adjusted	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.
- Higher clearance suggests potential induction of memantine metabolism due to concomitant AIDS drugs.

4.4 EXTRINSIC FACTORS

What extrinsic factors (herbal products, diet, smoking and alcohol) influence exposure and or response and what is the impact of any differences in exposure on pharmacodynamics?

The effect of extrinsic factors like herbal products, smoking and alcohol have not been conducted. Memantine is not metabolized by any of the CYP enzymes.

Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

The clearance of memantine is in part renal and dependent on tubular excretion. The drug-drug interaction studies conducted and planned are on drugs that also have the same elimination mechanism.
The drugs evaluated in the drug-drug interaction studies were hydrochlorothiazide/Triamterene (Dyazide®) and Donepezil (Aricept®). Studies ongoing are with glyburide/metformin (Glucovance®) and gabapentin (Neurontin®). Hydrochlorothiazide/Triamterene, metformin and gabapentin are all renally eliminated drugs where as donepezil could be used as an adjunct therapy in the treatment of dementia of the Alzheimer's type.

Influence of memantine on the pharmacokinetics of other drugs:

- **On Hydrochlorothiazide:** A 19 and 20%↓ in the Cmax and AUC0-24 of hydrochlorothiazide, respectively was observed after multiple daily doses of 20 mg memantine and 25 mg/50 mg hydrochlorothiazide/triamterene. The 90% CI was 74.6-88.9 and 74.8-85.2 for Cmax and AUC0-24 respectively. Therefore a slightly reduced diuretic effect may be possible when memantine is coadministered with hydrochlorthiazide.

Memantine did not influence the pharmacokinetics of any other drugs (triamterene, hydroxy triamterene or donepezil).

Influence of other drugs on the pharmacokinetics of memantine:

None of the drugs studied influenced the pharmacokinetics of memantine (hydrochlorothiazide, triamterene or donepezil)

Is there an in vitro basis to suspect drug-drug interaction?

No, there is no in vitro basis to suspect drug-drug interaction, but the in vitro studies were conducted with 1 donor and as such may not be representative of all the CYP isoenzymes.

The activities measured in the in vitro 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.

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.

Average in vivo steady state plasma concentration of memantine following administration of 20 mg daily dose were around 80 ng/mL (0.37 μM) based on the pharmacokinetics studies. 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.

The glucuronidation of 1-naphthol and the sulphation of 1-naphthol were not affected by the addition of memantine to the reaction. There was some degree of reduction in the glucuronidation of testosterone.

Is memantine an inhibitor or inducer of the CYP enzymes?

Memantine is not an inhibitor of the CYP enzymes at the therapeutic concentrations (see previous response. The induction potential of memantine on the CYP enzymes has not been investigated.

Is memantine a substrate of CYP enzymes?

Memantine is not metabolized by CYP 450 isoenzymes based on results from incubation of memantine with immortalized human liver epithelial cells (THLE) which were genetically manipulated to express specific CYP genes. The isoenzymes evaluated were CYP 1A2, 2E1, 3A4, 2B6, 2A6, 2C9, 2D6 and 2C19. The activity of the isoenzymes on memantine was measured by loss of memantine in these incubations. The loss of parent compound from these incubations were similar to the controls (Neo cells and 293 cells, that do not express any CYP at all).

Is memantine a substrate and/or inhibitor of p-glycoprotein transport processes?

There was no transport polarity in MDR-LLC-PK1 and wild type LLC-PK1 cells. The ratio of the amount transported to the apical side/amount transported to the basolateral side (A/B) was 1 after 1, 2, 3 and 4 hours in MDR-LLC-PK1. The A/B ratios showed a little increase, but were still close to 1 in wild type LLC-PK1 cells.

This indicated that memantine is not a substrate for MDR1-Pgp. In wild-type LLC-PK1cells there is no transporter for memantine that is quantitatively important in this cell line.

In another study the ratio of BL-AP permeability to AP-BL permeability is less than 1 indicating that there is no carrier mediated transport such as P-gp for memantine as shown in the following Table. These studies were conducted with parallel control studies involving efflux of 3H-vinblastine in both directions showing 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.

Memantine Donor Concentration	Memantine AP-BL Permeability x 10^{6} (cm/sec)	Memantine BL-AP Permeability x 10^{6} (cm/sec)
1.6 µg/ml	34.3 ± 0.7	31.4 ± 1.2
16 µg/ml	44.1 ± 1.6	34.6 ± 1.9
160 µg/ml	40.5 ± 2.4	32.3 ± 1.3

4.5 GENERAL BIOPHARMACEUTICS

Based on the BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

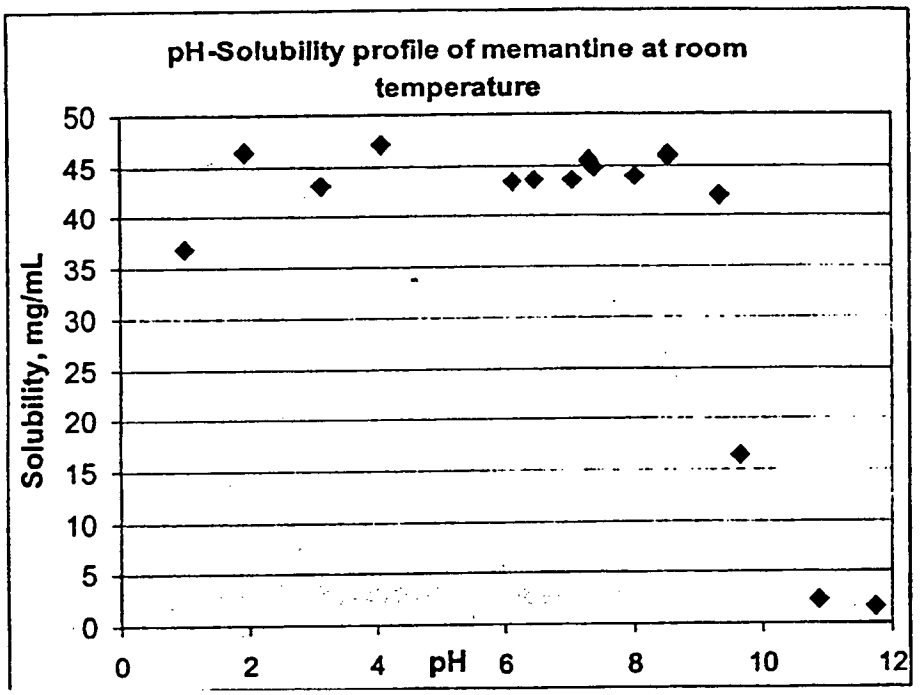
Memantine is highly soluble, highly permeable and rapidly dissolving drug and can be classified as a BCS Class I drug. The following information supports its classification:

Solubility:

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

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 in the entire pH range is shown in the following figure:



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 than this concentration in the pH range of 1-7.5.
Therefore, memantine can be classified as a highly soluble drug.

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 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. There was no indication of involvement of any efflux system. In all the cases, the permeability of memantine HCl was greater than the permeability of metoprolol (a marker for highly permeable compound), 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)

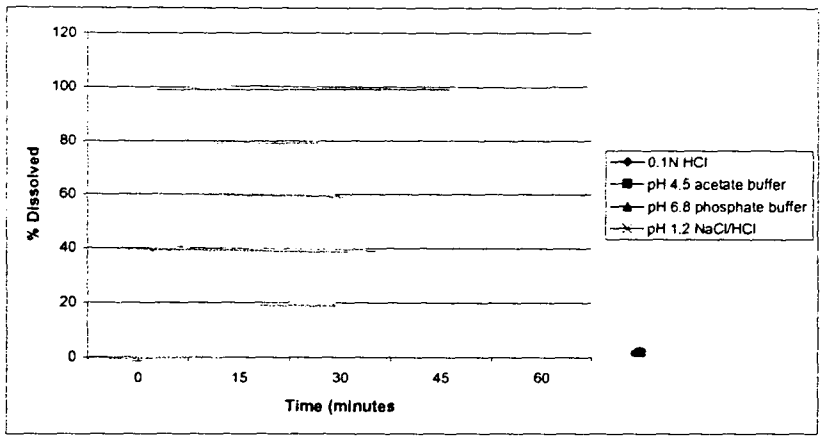
[a] Fluorescein permeability in the AB-BL and BL-AP directions were 5.73 (± 0.47) and 6.10 (± 0.34) x 10^{-6} cm/sec, respectively, indicating competent monolayers.
[b] Fluorescein permeability in the AB-BL and BL-AP directions were 2.77 (± 0.43) and 2.69 (± 0.04) x 10^{-6} cm/sec, respectively, indicating 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.

The permeability data was also reviewed and conclusions confirmed by Dr. Donna Volpe at the Division of Product Quality and Research (reviewed attached in Appendix IV)

The results indicate that memantine could be classified as a "highly permeable" drug according to the Biopharmaceutics Classification System guidance.

Dissolution:

More than —% is dissolved by — minutes, as shown in the following figure at various pHs.



Hence, memantine tablets can be considered as "rapidly dissolving".

Is the proposed to-be-marketed formulation of memantine bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

Memantine 10 mg tablets manufactured by Forest Laboratories were bioequivalent to the 10 mg tablets manufactured by Merz.

The pharmacokinetic parameters of memantine following administration of the Forest tablets (to-be-marketed) and the Merz tablets (clinical trial formulation) under fasted conditions are tabulated in the following Table.

Table:
Pharmacokinetic Parameters of Memantine Following Administration of 2 x 10 mg Forest Tablets Under Fasted Conditions and 2 x 10 mg Merz Tablets Under Fasted Conditions in Healthy Male and Female Subjects

Parameter	*Treatment A Forest, fasted (n=23)*	*Treatment B Merz, Fasted (n=23)*	*90% Confidence Intervals Treatment A vs. Treatment B (Forest vs. Merz)*
C_{max} (ng/mL)	24.4 ± 4.4	23.7 ± 3.6	98 – 105
AUC_{0-t} (ng h/mL)	1878.5 ± 468.1	1824.3 ± 450.2	95 – 102
$AUC_{0-\infty}$ (ng h/mL)	1939.7 ± 472.1	1881.2 ± 453.3	95 - 102
T_{max} (h)	5.6 ± 0.8	5.8 ± 0.7	-
$T_{1/2}$ (h)	55.6 ± 10.3	57.2 ± 10.9	-
CL/F (mL/min)	151.0 ± 36.0	155.1 ± 38.8	-
Vd/F (L)	846.7 ± 123.3	899.4 ± 155.9	-

There were no statistically significant differences in terms of Cmax and AUC parameters

following administration of the Forest and Merz tablets.

What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of memantine in relation to meals or meal types?

Food had no effect on the rate and extent of absorption of memantine following administration of 2 x 10 mg memantine tablets manufactured by Forest Laboratories, Inc. Memantine can be dosed without regard to food. The Clinical trials were conducted without regard to food.

The pharmacokinetic parameters of memantine following administration of the Forest tablets under fasted and fed conditions are tabulated in the following Table.

Table:
Pharmacokinetic Parameters of Memantine Following Administration of 2 x 10 mg Forest Tablets Under Fasted and Fed Conditions in Healthy Male and Female Subjects

Parameter	*Treatment A Forest, fasted (n=23)*	*Treatment B Forest, Fed (n=23)*	*90% Confidence Intervals Treatment B vs. Treatment A (Fed vs. Fasted)*
C_{max} (ng/mL)	24.4 ± 4.4	24.7 ± 4.4	99 – 106
AUC_{0-t} (ng h/mL)	1878.5 ± 468.1	1840.4 ± 435.9	99 – 107
$AUC_{0-\infty}$ (ng h/mL)	1939.7 ± 472.1	1898.7 ± 444.3	100 - 107
T_{max} (h)	5.6 ± 0.8	5.0 ± 2.0	-
$T_{1/2}$ (h)	55.6 ± 10.3	55.9 ± 10.7	-
CL/F (mL/min)	151.0 ± 36.0	153.7 ± 29.1	-
Vd/F (L)	846.7 ± 123.3	868.1 ± 143.7	-

How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

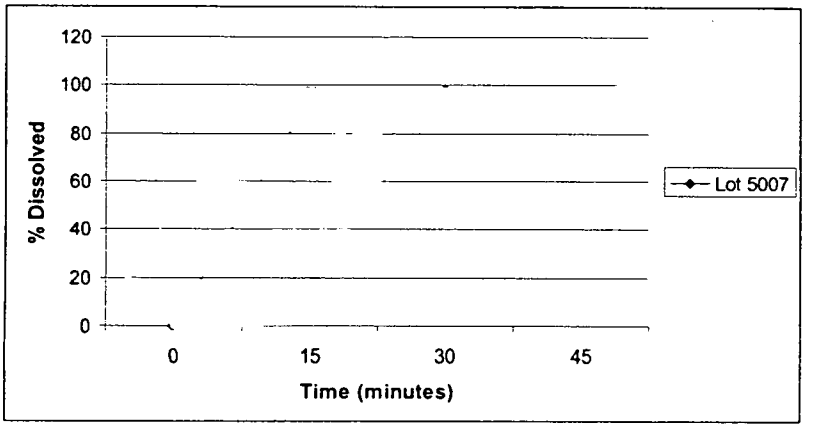
Method:

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: 5-10 mL aliquots
Sampling Time: [redacted]

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

Q= —% at 30 minutes

The dissolution profile of the Forest Formulation Lot 5007 used in the Pivotal BE study is given below:



4.6 ANALYTICAL

What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

Three main methods were used to determine memantine in human plasma and urine. These are decribed below along with their acceptability and completeness.

Method 1

— monitored by . — (Report 6868-610/7-date May-August 1991)

Lower Limits of Quantitation

	Plasma	Urine
Memantine	—	ng/ml

Plasma:
Linear Range: — ng/ml in plasma
Intra-day precision: — % CV
Inter-day precision: — % CV
Quality control concentrations:
Inter-day accuracy and precision for QC: — % of the nominal concentration.
Stability:

(*mentioned in summary of the report, but no data, duration etc given. The sponsor clarified that these samples were stable for — hours in the —)

Long term stability: —

Sensitivity: no interference

Urine:
Linear Range: —
Intra-day precision: — % CV
Inter-day precision: — % CV
Quality control concentrations: —
Inter-day precision: — % CV
Inter-day accuracy: — % of the nominal concentration
Stability:
—

Sensitivity: no interference

Assay validation acceptable

Method 2

— derivatization(Report ZA008-01-date September 1996)

Lower Limits of Quantitation

	Plasma	Urine
Memantine	—	ng/ml

Plasma:
Linear Range: —
Linear Range —
Quality control concentrations: —
Intra-day precision for QC: —
Inter-day precision: — % CV
Accuracy: — % of the nominal concentration
Stability: — CV — %
— % CV — %
— % CV — %

Sensitivity: no interference

Urine:
Linear Range: — ng/ml in urine
Quality control concentrations: — ng/ml
Intra-day precision for QC: — % CV
Intra-day Accuracy : — %
Inter-day precision: — % CV
Inter-day Accuracy : — %
Stability: — — %
— % CV — %
— % CV — %

Sensitivity: no interference

Assay validation acceptable.

Method 3

(Report 206-date November 2001)

Lower Limits of Quantitation

	Plasma
Memantine	ng/mL

Plasma:
Linear Range: ng/ml in plasma
Quality control concentrations: ng/ml
Intra-day and Inter-day precision for QC: within % deviation, 3 outliers % deviation
for the ng/ml solution
Intra-day and Inter-day accuracy: within % deviation
Stability: % deviation
% deviation
% deviation

Sensitivity: no interference
Recovery: %

Assay validation acceptable

Method 4

(this is modified method 2)(Report MBC98N168-date October 1999)

Lower Limits of Quantitation

	Plasma	Urine
Memantine		ml

Plasma:
Linear Range: ng/ml in plasma
Quality control concentrations: ng/ml
Intra-day precision for QC: % CV
Inter-day precision: CV
Stability: , % CV
% CV
% CV
months, % CV
internal standards and solution for month, % CV
Sensitivity: no interference

Urine:
Linear Range: ng/ml in urine
Quality control concentrations: ng/ml
Intra-day precision for QC: CV

Inter-day precision: % CV
% CV <
% CV
% CV
% CV
internal standards and solution for month, % CV
Sensitivity: no interference

Assay validation acceptable

Method 5

Lower Limits of Quantitation

	Plasma	Urine
Memantine		ng/ml

Plasma:
Linear Range ng/ml
% recovery in plasma: %
Accuracy in plasma of standards: %

Urine
Linear Range ng/ml
% recovery in urine: %
Accuracy in urine of standards: % of the nominal value in urine

No other parameters provided, assay not acceptable

Method 6

(Report DSU 95-A039-date August 1996)

Lower Limits of Quantitation

	Plasma
Memantine	ng/mL

Plasma:
Linear Range: ng/ml in plasma
Quality control concentrations: ng/ml
Intra-day precision for QC: % CV
Inter-day precision: % CV
Stability: % deviation
% deviation
% CV
% deviation
% deviation
Sensitivity: no interference
Extraction recovery: %

Assay validation acceptable.

OVERALL STABILITY:

Long-term

- Upto — years at — for plasma and urine using — methodology
  The % accuracy for the stored samples appeared to be between — % of the theoretical concentration.

- plasma samples up to — days at — using — methodology, % difference between — . Urine samples up to — days at — using — methodology, % difference between —

Room Temperature:

- Up to — hours in — for method 1
- Up to — hours for method 2
- Up to — hours for method 3

APPEARS THIS WAY
ON ORIGINAL

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

6.0 APPENDIX

6.1 APPENDIX I

INDIVIDUAL STUDY REVIEW

ADME STUDIES

SINGLE DOSE STUDIES

Study: HUK-610/4: ***Memantine pharmacokinetics, dose-relationships and absolute bioavailability for single oral doses of 10, 20 and 40 mg in comparison with single IV solution.***

Objectives:

(a) To determine the absolute bioavailability of single oral doses of 10, 20 and 40 mg memantine,
(b) To assess dose proportionality for oral doses of 10, 20 and 40 mg memantine and
(c) To provide further pharmacokinetic information on the absorption and disposition of memantine after oral and intravenous dosing.

The study design is as follows:

Study Design	Open label, randomized, 4-way crossover study
Study Population	N=12 Healthy subjects Age: 20-39 years (mean age 27 years) Gender: 12 males Weight: 63.7-81.2 kg (mean 75.3 kg) Race: 11 Caucasian, 1 Asian
Treatment Group	A: 1 x 10 mg memantine tablet (actual dose of memantine free-base 8.14 mg) B: 2 x 10 mg memantine tablet (actual dose of memantine free-base 16.29 mg) C: 4 x 10 mg memantine tablet (actual dose of memantine free-base 32.58 mg) D: 20 mg intravenous dose, 10 mg/h for 2 hours (actual dose of memantine free-base 15.56 mg)
Dosage and Administration	Tablets administered with 150 mL of water and intravenous memantine was infused over 2 hours 10 mg memantine, batch 90101 memantine ampoules, batch 90502 Diet: Following an overnight fast a light breakfast was provided 0.5 hour prior to dosing. Lunch, evening meal and evening snack were provided 4, 10 and 14 hours after oral administration/start of infusion. Washout: 21-day washout between two treatments
Sampling: Blood	After oral dosing: At predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, and 192 hours post dose After IV dosing: additional extra samples at 2 hr 5 min, 2 hr 10 min, 2 hr 20 min, 2 hr 30 min and 10 hr after the start of IV infusion of 20 mg

	memantine
Urine	At predose, 0-4 hr, 4-8 hr, 8-12 hr, 12-24 hr, 24-36 hr and 36-48 hr after treatment
Feces	none
Analysis	[redacted] (Report 6868-610/7) Lower Limits of Quantitation Plasma Urine Memantine [redacted] ng/mL [redacted] ng/ml Plasma: Linear Range: [redacted] ng/ml in plasma Quality control concentrations: [redacted] (The QC sample [redacted] ng/ml was diluted [redacted] using control plasma prior to analysis) Inter-day precision: [redacted] % CV Inter-day accuracy: [redacted] % of the nominal concentration Stability: [redacted] Sensitivity: no interference Urine: Linear Range: [redacted] ng/ml in urine Quality control concentrations: [redacted] ng/ml (The QC sample [redacted] ng/ml was diluted [redacted] using comtrol plasma prior to analysis) Inter-day precision: [redacted] % CV Inter-day accuracy: [redacted] % of the nominal concentration Stability: [redacted] Sensitivity: no interference Assay performance complete and acceptable (see reviewer's comment)
PK Assessment	AUC0-t, AUC0-∞,Cmax, Tmax, t1/2, Kel, CL, MRT, Ae(0-48), F, Molecular weight ratio for calculating memantine free base=0.831
Safety Assessment	Laboratory tests, adverse events
PD Assessment	None

Pharmacokinetic Results:

Plasma:

- Following oral administration of 10 mg memantine, plasma drug concentrations were detectable in all subjects from 3-24 hours. At this dose the concentrations of memantine were close to the LLOQ [redacted] ng/ml) and there were series of irregular secondary peaks for the individual concentration-time profiles, hence the reliability of this data and the corresponding pharmacokinetic parameters are questionable. The plasma concentrations at the elimination phase were close to LLOQ, hence, the accuracy of the half-life data is also questionable. Half-life was only calculated for 2 subjects. A large portion of AUC0-∞ relied on the half-lives as well therefore this parameter does not provide much reliability either and was only calculated in 2 subjects. The calculation of F and MRT also depended on AUC0-∞ values, therefore should be treated with caution. A total of 4 predose plasma samples also had

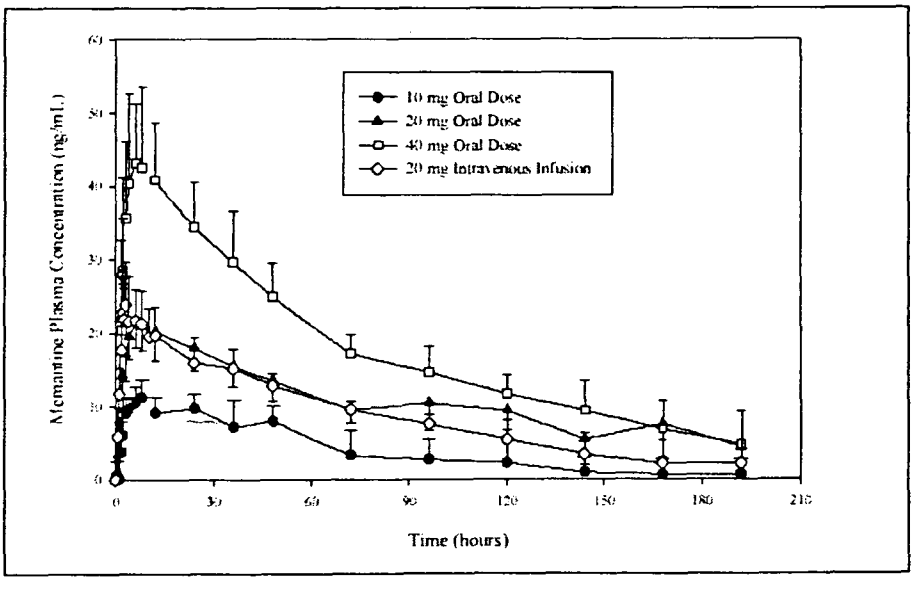
detectable amounts of memantine reported with values ranging from — ng/ml. The accuracy and reliability of this data is questionable.

- Following oral administration of 20 mg memantine, plasma drug concentrations were detectable in all subjects from 2-120 hours.
- Following oral administration of 40 mg memantine, plasma drug concentrations were detectable in all subjects from 2-144 hours. The analytical variability was lower at this dose.

The mean (SD) pharmacokinetics parameters are shown in the following Table:

Parameter	10 mg Oral Dose (n=12)	20 mg Oral Dose (n=12)	40 mg Oral Dose (n=12)	20 mg Intravenous Infusion (n=12)
C_{max} (ng/mL)	12.17 ± 2.20	22.10 ± 3.71	47.98 ± 10.94	28.70 ± 7.37
C_{max} (adjusted)[a]	1.495 ± 0.270	1.357 ± 0.228	1.473 ± 0.336	1.844 ± 0.473
T_{max} (h)	19.3 ± 21.9	7.7 ± 5.6	5.9 ± 3.0	2.3 ± 0.6
AUC_{0-t} (ng h/mL)	658 ± 296	1989 ± 431	3307 ± 633	1593 ± 299
AUC_{0-t} (adjusted)[a]	80.85 ± 36.39	122.11 ± 26.48	101.49 ± 19.43	102.37 ± 19.20
$AUC_{0-\infty}$ (ng h/mL)	1567 ± 357[b]	2939 ± 584[c]	4269 ± 787	2220 ± 546
$AUC_{0-\infty}$ (adjusted)[a]	192.47 ± 43.81[b]	180.42 ± 35.82[c]	131.03 ± 24.15	142.65 ± 35.11
$T_{1/2}$ (h)	101.0 ± 28.7[b]	104.1 ± 13.5[c]	83.2 ± 18.4	73.7 ± 25.0
MRT (h)	142.9 ± 36.1[b]	147.4 ± 17.7[c]	116.9 ± 25.0	113.4 ± 39.8
F (%)	148.9 ± 78.8[b]	120.4 ± 25.2[c]	97.0 ± 29.6	-
CL (mL/min)	-	-	-	122.81 ± 27.35
Vd(L/kg)	-	-	-	9.88 ± 2.12
V_{ss} (L/kg)	-	-	-	10.63 ± 3.15
Ae_{0-48} (µg)	1234 ± 488	2869 ± 1036	5798 ± 2563	3139 ± 1089
Ae_{0-48} (adjusted)[a]	151.7 ± 59.9	176.1 ± 63.6	178.0 ± 78.7	201.8 ± 70.0
fe (%)	15.2 ± 6.0	17.6 ± 6.4	17.8 ± 7.9	20.2 ± 7.0
CL_r (mL/min)	50.35 ± 16.84	61.63 ± 27.45	63.91 ± 29.88	68.23 ± 30.46
[a] Pharmacokinetic parameter values divided by actual free-base dose				
[b] Based on n=2				
[c] Based on n = 8				

The mean plasma concentration-time profile after single dose of the four treatments is shown in the following figure:



- Mean peak plasma concentration occurred between 6-8 hours. The mean Tmax after the 10 mg dose was 19.3 hr (range ——— . The range for the 20 mg dose was ——— hrs and for the 40 mg dose was ——— hrs.
- The absolute bioavailability was 149% for the 10 mg dose (range 93-205%, data from only 2 subjects), was 120% for the 20 mg dose (range 79-146%) and 97% with the 40 mg dose of memantine (range 50-157%). There were 5 subjects out of 12 that had a F >than 100 even with the 40 mg dose and 5 subjects with a F < 90% with the 40 mg dose. Estimation of mean absolute bioavailability was based on a total of 8 and 12 subjects, respectively for the 20 and 40 mg dose groups. An estimation of absolute bioavailability using AUC0-t also showed that the 20 mg dose had an absolute bioavailability of 125%. Therefore, the increase in bioavailability cannot be explained merely on levels being below the LLOQ. Some of the other postulates regarding this increase in bioavailability could be (a) a large portion of AUC0-∞ is extrapolated (b) non linearity at the lower doses (with three doses this could not accurately be ruled out), (c) reabsorption at alkaline urine pH (subjects were in house for the first 48 hours of the study).

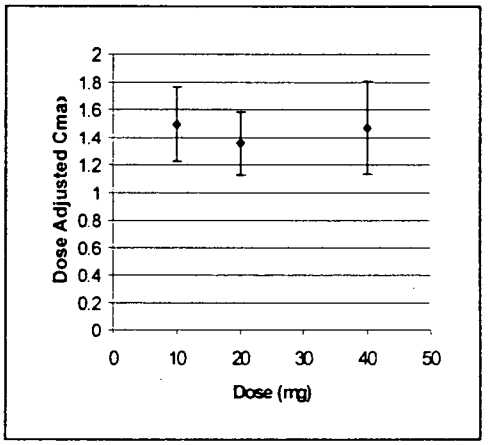
  A bioequivalence test shows the following results. The geometric mean ratios and the 90% confidence intervals are given below:

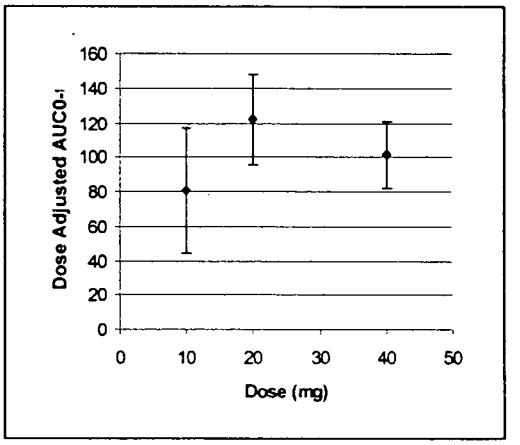
Treatment	AUC0-inf (dose adj)	Cmax (dose adj)
20 mg oral/20 mg IV	1.20 1.00-1.44	0.75 0.67-0.85
40 mg oral/20 mg IV	0.93 0.80-1.08	0.81 0.72-0.91

  Based on this bioequivalence test the dose adjusted AUC0-inf for 40 mg oral dose can be considered similar to the 20 mg IV dose. However, the 20 mg oral dose still gives a 20% higher exposure compared to the IV dose. These results cannot be explained based on the results provided.

- The mean half-lives ranged from 74-104 hours, however, the half-life calculation at the lower doses may not be very accurate.
- Following intravenous infusion, the volume of distribution during elimination phase (Vd) and at steady state (Vss) averaged 9.9 and 10.6 L/kg, respectively, suggesting extensive distribution into tissues.
- The difference between the total plasma CL (mean 122 ml/min) and renal CL (mean 68 ml/min) indicates that approximately 44% of the systemically available drug is cleared non-renally. It would be expected that a large portion of the non renal Cl is hepatic. Hepatic blood flow is 1500 ml/min, therefore it appears that memantine has a low extraction ratio in the liver and will not undergo extensive first pass metabolism, which is seen by the high oral bioavailability.
- The 10 mg pharmacokinetic parameters were not reliable enough to be included in the assessment of dose-proportionality. An analysis (Tukey Kramer Test) done by the sponsor shows that the AUC0-t was significantly different between the doses

(p=0.0013). The dose adjusted AUC0-t for the 20 mg dose was about 20% higher than the 40 mg dose.
However, the dose-adjusted Cmax was similar for the 20 and 40 mg dose. A graphical representation is given below.

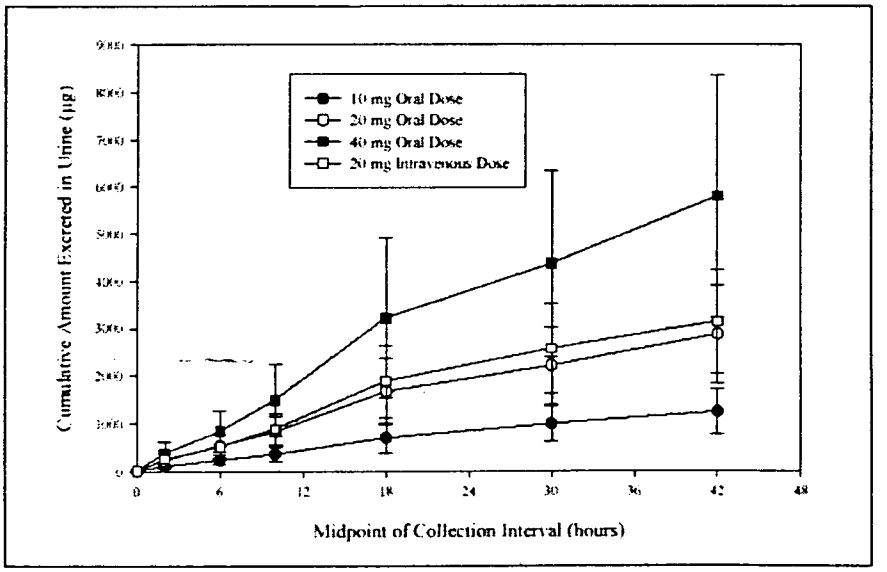




A power analysis conducted by the reviewer to assess dose proportionalilty showed that the pharmacokinetic parameters were dose proportional (estimate close to 1 and the 95% CI included 1). The 10 mg dose was also included in the analysis.

Parameter	Estimate	95% CI
AUC0-t	1.21	0.89-1.35
Cmax	0.985	0.85-1.12

Urine:
Memantine urine levels were much above the limit of quantitation. One predose sample had a detectable level of —ng/ml. The mean cumulative amount of memantine excreted in the urine following oral and intravenous doses is shown in the following figure:



- The amount of memantine excreted in the urine increased with the increase in oral dose of memantine. The urinary parameters are given in the Table along with the plasma memantine parameters.
- Similar excretion profiles were obtained following administration of 20 mg memantine as oral and intravenous doses.
- During the 48 hour urine collection, between 15.2-17.8% of the oral dose and 20% of the IV dose was excreted as unchanged drug.
- Looking at the figure it appears that some reabsorption is taking place, however, memantine is a highly polar compound. Mechanism of renal elimination is unexplained at this time.

Reviewer's Comment:

- *The sponsor had not provided any long term storage stability data for the assay validation. The sponsor should have at least 2 months long term stability data. Some samples were stored at - — Room temperature stability data has also not been provided for both plasma and urine analysis.*
- *Based on the sponsor's response to the above mentioned stability of sample issues, the sponsor provided additional data to show that memantine was stable in human plasma for — The samples took — for analysis and during this time did not show any degradation in the vial. Based on these responses the assay validation issues are resolved for this study*

Conclusions:

Absolute Bioavailability:

- No definite conclusions can be drawn regarding the absolute bioavailability from this study. The 10 mg data was not reliable at all, as many subjects had levels below the LLOQ. Most subjects at the 20 and 40 mg dose levels had memantine levels above the LLOQ, yet the absolute bioavailability for the 20 mg dose was 120%. These results cannot be explained from the data. High variability was also observed in the absolute bioavailability values for the 40 mg dose group, with a mean of 97% (range 50-157%).
- The high bioavailability observed in this case appears to be an artifact of the study design. Some of the plausible reasons could be that (a) the plasma samples were not taken long enough (say close to 5 half-lives). Samples were taken only up to 2.5 half-lives. A large portion of the AUC0-∞ was extrapolated. However, bioavailability calculations on AUC0-t also gave bioavailabilities greater than 100. (b) Another reason could be that the diet of the subjects was not controlled during the entire sampling period. The diet was regulated only up to the 48 hour sample. Alkaline urine can cause the renal clearance to be reduced as a result of tubular reabsorption leading