- Mean bile memantine concentrations 11.04 and 15.45 mg/l in HD males and females, respectively, at end of study, negative in bile after recovery
- Organ concentrations: lung (14.29 in males, 21.41 in females), eye (13.06 in males, 16.73 in females), urine (8.81 in males, 8.42 in females), liver (6.96 in males, 10.20 in females), spinal cord (5.19 in males, 5.26 in females), brain (3.64 in males, 4.66 in females), feces (2.47 in males, 2.68 in females), lachrymal gland (1.57 in males, 2.67 in females), parotid gland (1.32 in males, 2.13 in females), and prostate gland (0.68 in males); after recovery memantine detected in eye only (0.96 mcg/g)
- No definitive target organs of toxicity
- Memantine well tolerated by the baboons at up to 8 mg/kg/day (approximately 3X-13X the MRHD of 20 mg in a 60 kg patient on a BSA basis)

Study no: PTX 48/8854
Volume # 37, and page # 1
Conducting laboratory and location:

Date of study initiation: July 8, 1986
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug Memantine HCl, **lot #** R 7979, **radiolabel** Not applicable, **and % purity** 99.8%
Formulation/vehicle: Test article dissolved in distilled water, formulation confirmed by sampling and chemical analysis in weeks 1, 13, 26, and 52

Methods (unique aspects):
Dosing:

Species/strain: Wild baboons
#/sex/group or time point (main study): 4/sex/dose
Satellite groups used for toxicokinetics or recovery: 2/sex/dose recovery groups (control and high dose only),
Age: 2-4 years
Weight: 3-6 kg
Doses in administered units: 0, 2, 4, and 8 mg/kg/day
Route, form, volume, and infusion rate: Oral by gastric intubation, once daily for 52 weeks, at 4 ml/kg, 1 hour before availability of food

Observations and times:

Clinical signs: Daily, 2X daily during recovery period
Body weights: Weekly, daily during 1st week of recovery period and weekly thereafter
Food consumption: Daily
Ophthalmoscopy: Weeks 0 (before dosing) and 13, 26, and 51, and end of recovery period
EKG: Not done
Hematology: Weeks 0 (before dosing) and 13, 26, and 51, and end of recovery period
Clinical chemistry: Weeks 0 (before dosing) and 13, 26, and 51, and end of recovery period
Urinalysis: 16-hour collection period in Weeks 0 (before dosing) and 13, 26, and 51, and end of recovery period
Gross pathology: End of 52-week dosing period and end of 4-week recovery period

Organs weighed: End of 52-week dosing period and end of 4-week recovery period, see under Histopathology Inventory, below
Histopathology: End of 52-week dosing period and end of 4-week recovery period, see under Histopathology Inventory, below
Toxicokinetics: Blood (4 ml) withdrawn from all baboons before dosing (24 hours after dosing) in dosing weeks 0, 13, 26, and 52, and recovery weeks 2, and 4
Other: Tissue memantine levels: serum, bile, urine, rectal feces, pieces of spinal cord, brain (pons), lung, liver, lachrymal gland, parotid gland, prostate, and eye

Results:

Mortality: No deaths
Clinical signs: Treatment-related effects:
Vomiting beginning 45 minutes after dosing, in 9 HD, 2 MD, and 1LD animal during first few days of dosing (% incidence per total doses during study: 0.32, 0.21, 0.52, and 0.64 at 0, 2, 4, and 8 mg/kg/day, respectively, 2912-4368 doses given)
Quietness with highest incidence at the HD, during first 26 weeks (% incidence during study: 1.47, 6.49, 7.90, and 23.49 at 0, 2, 4, and 8 mg/kg/day, respectively)
Ptosis dose related (% incidence during study: 0, 8.55, 75.24, and 95.86 at 0, 2, 4, and 8 mg/kg/day, respectively)
Huddled posture with highest incidence in HD animals during first weeks of dosing (% incidence during study: 0.14, 0.24, 0.10, and 1.42 at 0, 2, 4, and 8 mg/kg/day, respectively)
No treatment-related effects on body temperature
Body weights: No treatment related effects on body weights except for reduction in the first dosing week at 4 and 8 mg/kg/day, reduction in mean body weights when averaged over weeks 0-52 not statistically significant (12% and 6% in MD and HD males, respectively, and 14%, 15%, and 6% in LD, MD, and HD females, respectively)
Food consumption: No treatment-related effects
Ophthalmoscopy: No treatment-related effects
Electrocardiography: Not done
Hematology: Changes in red cell indices including:
PCV (Decreased 3% at HD in Wk 26)
Hb (Decreased 5% at HD in Wk 51)
MCHC (Decreased 2%, 7%, and 7% at LD, MD and HD, respectively, in Wk 51)
MCV (Increased 10% and 6% at MD and HD, respectively, in Wk 51)
WBC (Increased 26% at HD in Wk 51)
Neutrophils (Increased 83% at HD in Wk 51)
All values within range of historical control values, effects not considered to be treatment-related, No treatment-related effects observed after the recovery period
Clinical chemistry: The following changes were observed:
Serum protein (Decreased 4% at HD in Wk 13, 6% at MD and 4% at HD in Wk 26)
Albumin (Decreased 4% at HD in Wk 26, Increased 10% at HD in Wk 51)
Alpha2 globulin (Decreased 33% at LD, MD and HD in Wk 51)
Beta globulin (Decreased 20% at LD, MD and HD in Wk 13, 18% at LD and MD and 9% at HD in Wk 51)
Globulin (Decreased 13% at MD and HD in Wk 13, 14%-21% at LD, MD and HD in Wk 51)
Thyroxine (T3 Increased 22% at HD in Wk 13, T4 Decreased 22% at HD in Wk 51)

Cortisol (Decreased 27% at HD in Wk 51)
Changes in serum proteins were not dose-related, were within range of historical control values or were not observed in Wk 51, serum thyroxine changes were without corresponding changes in organ weights and histopathology, and cortisol level changes not significant or dose-related at lower dose levels), no changes considered to be of toxicological significance

Urinalysis: No treatment-related effects
Organ weights: No treatment-related effects at the terminal and post-recovery examinations
Gross pathology: No treatment-related effects after the 52-week treatment period; pale raised foci on the mucosal surface of the stomach fundus, red/dark mucosal discoloration in mucosal tissue in body/fundus in stomachs of both HD females after the 4-week recovery period
Histopathology: Moderate increases in erythroid cells in 1 MD female and 1 HD male and 2 HD female baboons, without anemia or microscopic pathology indicating marrow stimulation, and no differences from controls after the recovery period; lymphoid foci in the stomach mucosa in both HD females after the recovery period, submucosal hemorrhage in one HD female after recovery, known to occur in control baboons, not considered to be of toxicological significance
Toxicokinetics: The plasma memantine levels are presented in the following table:

Mean Plasma Memantine in Baboons Treated by Oral Gavage Daily for 52 Weeks (mcg/l)

Study Week	2 mg/kg/day		4 mg/kg/day		8 mg/kg/day	
	Males	Females	Males	Females	Males	Females
13	10.2	6.8	20.6	19.9	82.6	94.6
26	7.9	5.1	19.0	20.0	68.5	94.1
52	7.6	6.7	15.4	15.7	60.4	83.3
Terminal	-	-	-	-	67.6	88.6
Recovery	-	-	-	-	0	0

The mean bile memantine concentrations were 11.04 and 15.45 mg/l in the males and females given 8 mg/kg/day memantine HCl, respectively, at the end of the study. No memantine was found in bile after the 4-week recovery period. Measurements of organ tissue concentrations (mcg/g) of memantine in the high dose animals showed test article in the lung (14.29 in males, 21.41 in females), eye (13.06 in males, 16.73 in females), urine (8.81 in males, 8.42 in females), liver (6.96 in males, 10.20 in females), spinal cord (5.19 in males, 5.26 in females), brain (3.64 in males, 4.66 in females), feces (2.47 in males, 2.68 in females), lachrymal gland (1.57 in males, 2.67 in females), parotid gland (1.32 in males, 2.13 in females), and prostate gland (0.68 in males). Memantine was detected in the eye only, at a mean concentration of 0.96 mcg/g after the 4-week recovery period.

Histopathology Inventory for NDA # 21-487

Study	6196/92 13-wk	442/003 13-wk	B-1717 13-wk	46/861238 13-wk	N002171A 6-mo	244006 6-mo	12-mo	442/007 12-mo	12-mo	48/8854 12-mo	7279/92 113-wk	7280/92 129-wk
Species	Mouse	Rat	Rat	Baboon	Rat	Dog	Rat	Rat	Dog	Baboon	Mouse	Rat
Adrenals	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Aorta	X	X	X	X	X	X		X	X	X	X	X
Bone Marrow smear	X	X	X		X	X	X	X	X	X	X	X
Bone (femur)	X	X	X	X	X	X		X		X	X	X
Brain	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Cecum	X	X	X	X	X	X		X		X	X	X
Cervix	X										X	
Colon	X	X	X	X	X	X	X	X	X	X	X	X
Duodenum	X	X	X	X	X	X		X	X	X	X	X
Epididymis	X*	X	X*	X*	X	X	X	X	X	X*	X*	X*
Esophagus	X	X	X	X	X	X		X		X		
Eye	X	X	X	X	X	X		X		X	X	X
Fallopian tube												
Gall bladder	X			X		X			X	X	X	
Gross lesions		X	X		X	X		X			X	X
Harderian gland	X		X								X	X
Heart	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Ileum	X	X	X	X	X	X		X		X	X	X
Injection site												
Jejunum	X	X	X	X	X	X		X	X	X	X	X
Kidneys	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Lachrymal gland				X	X	X						
Larynx											X	X
Liver	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Lungs	X*	X	X*	X*	X	X*	X	X	X	X*	X*	X*
Lymph nodes, cervical			X	X					X	X	X	X
Lymph nodes mandibular or submaxillaris	X*	X			X	X		X			X*	X*
Lymph nodes, mesenteric		X	X	X	X	X		X	X	X	X	X
Mammary Gland	X	X	X	X	X	X		X		X	X	X
Nasal cavity	X										X	X
Optic nerves	X		X		X	X		X			X	X
Ovaries	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Pancreas	X	X	X	X*	X	X		X	X	X*	X	X*
Parathyroid	X	X	X	X	X*	X		X		X	X	X
Peripheral nerve						X						
Pharynx	X										X	
Pituitary	X*	X*	X*	X*	X	X*		X*		X*	X*	X*
Prostate	X	X*	X*	X*	X*	X*	X*	X*	X*	X*	X	X*
Rectum	X	X	X	X	X	X		X		X	X	X
Salivary gland	X	X	X*	X*	X	X*		X		X*	X	X
Sciatic nerve	X	X	X	X	X			X		X	X	X
Seminal vesicles		X	X	X*	X			X		X*	X	X*
Skeletal muscle	X	X	X	X	X	X		X	X	X	X	X
Skin	X	X	X	X	X	X		X		X	X	X

Spinal cord	X	X	X	X	X	X		X	X	X	X	X
Spleen	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Sternum		X	X	X	X			X		X	X	X
Stomach	X	X	X	X	X	X		X	X	X	X	X
Testes	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Thymus	X*	X*	X*	X*	X	X*		X*		X*	X*	X*
Thyroid	X*	X*	X	X*	X*	X*	X	X*	X*	X*	X*	X*
Tongue	X	X	X	X	X	X		X		X	X	X
Trachea	X	X	X	X	X	X	X	X		X	X	X
Urinary bladder	X	X	X	X	X	X		X	X	X	X	X
Uterus	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Vagina	X		X	X	X	X		X		X	X	X
Zymbal gland												
Standard List												
Costochondral junction(rib)												X
Ear(internal and external)												X
Mesovary/mesometrium												X

X, histopathology performed
* organ weight obtained

V. GENETIC TOXICOLOGY:

Study title: Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of Memantine

Key findings:

- Memantine HCl was negative for mutagenicity in *Salmonella typhimurium* (Ames test) at concentrations from 250-2000 mcg/plate under the conditions tested
- However, there was insufficient description of the methods, test article purity and stability, counting method, and incubation times, no replicates were assayed, incubation and sampling times were not provided, criteria for positive results were not described, and tester strains with the AT base pair (e.g., *E. coli* WP2 and *S. typhimurium* TA 102) at the primary reversion site were not evaluated, and therefore the study is considered to be not valid

Study no: PTX 8/80764
Study type: Mutagenicity: to detect induction of DNA base pair substitution and frameshift mutations (Ames *et al.*, Mutation Res. 31:347-364, 1975)
Volume # 61, and page # 210
Conducting laboratory and location: ——

Date of study initiation: Not provided, Report date November 19, 1980
GLP compliance: yes (x) no ( )
QA reports: yes (x) no ( )
Drug Memantine HCl, **lot # 17, radiolabel** Not applicable, **and % purity** Not provided

Formulation/vehicle: Test article dissolved in sterile distilled water

Methods:

Strains/species/cell line: *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100

Dose selection criteria:

Basis of dose selection: Test article soluble at up to the acceptable top concentration of 5 mg/plate, Dose-range finding test conducted

Range finding studies: Test article added to bacterial strains in histidine-biotin-rich medium at 0, 10, 100, 1000, and 10,000 mcg/plate, with and without metabolic activation with S9: Results showed excessive cytotoxicity at 10,000 mcg/plate in TA 1535, TA 1537, TA 98, and TA 100 (no bacterial lawn observed), and at all concentrations tested in TA 1538 (incomplete bacterial lawn). The results of the dose-range finding test are presented in the following table:

Dose-Range Finding Study on Memantine in *S. typhimurium*: Revertant Colony Numbers

Memantine Concentration (mcg/plate)	Metabolic Activation	*S. typhimurium* Strain				
		TA 1535	TA 1537	TA 1538	TA 98	TA 100
10,000	-	NL	NL	NL	NL	NL
1,000	-	22	7	IL	22	84
100	-	21	7	IL	35	89
10	-	24	10	IL	28	95
0	-	25	11	11	20	84
10,000	+	IL	IL	IL	IL	IL
1,000	+	12	14	IL	22	84
100	+	22	12	IL	39	85
10	+	10	8	IL	33	98
0	+	8	9	18	22	113

NL: no lawn; IL: incomplete lawn

Test agent stability: Not provided

Metabolic activation system: Liver microsome fraction (S9 mix)

Controls:

Vehicle: Sterile distilled water

Negative controls: Sterile distilled water, S9 mix

Positive controls: Sodium azide (5 mcg/plate) without S9 in TA 1535 and TA 100, 4-nitro-o-phenylene-diamine (250 mcg/plate, without S9 in TA 1537, TA 1538, and TA 98), 2-amino-anthracene (2 mcg/plate, with S9 in TA 1535, TA 98, and TA 100), Neutral red (10 mcg/plate, with S9 in TA 1537), 2-acetyl-aminofluorene (20 mcg/plate, without S9 in TA 1538),

Comments: Selected controls appropriate, tested in parallel with and without S9, assay conducted in triplicate

Exposure conditions:

Incubation and sampling times: Not provided

Doses used in definitive study: 0, 250, 500, 1000, 2000 mcg/plate

Study design: Not provided, sponsor stated that methods are described in Protocol MCB 101

Analysis:

No. of replicates: None
Counting method: Not provided
Criteria for positive results: Not provided

Summary of individual study findings:

Study validity: There was insufficient description of the methods, test article purity and stability, counting method, and incubation times; no replicates were assayed; incubation and sampling times were not provided; criteria for positive results were not described; tester strains with the AT base pair (e.g., *E. coli* WP2 and *S. typhimurium* TA 102) at the primary reversion site were not evaluated.

Study outcome: Memantine was cytotoxic at the high dose in all strains in the absence of metabolic activation with S9, and in TA 98 in the presence of S9. There were no statistically significant increases in revertant colony counts in any strain tested, with and without S9, at any dose tested from 250 – 2000 mcg/plate. Although memantine HCl was negative in the Ames test under the conditions of this study, the study is considered to be invalid because there was insufficient description of the methods, test article purity and stability, counting method, and incubation times, no replicates were assayed, incubation and sampling times were not provided, criteria for positive results were not described, and tester strains with the AT base pair (e.g., *E. coli* WP2 and *S. typhimurium* TA 102) at the primary reversion site were not evaluated.

Study title: Reverse Mutation Test of Memantine Hydrochloride in Bacteria

Key findings:
- Memantine HCl was negative in the Ames test at concentrations of up to 5000 mcg/ml in the absence and presence of metabolic activation using S9 mix, under the conditions of this study

Study no: 89101M
Study type: Mutagenicity: to detect induction of DNA base pair substitution and frameshift mutations (Ames *et al.*, Mutation Res. 31:347-364, 1975)
Volume # 61, and page # 221
Conducting laboratory and location: [redacted]

Date of study initiation: January 30, 1989
GLP compliance: yes (x, Japan) no ( )
QA reports: yes (x) no ( )
Drug Memantine HCl, **lot #** R1452, **radiolabel** Not applicable, **and % purity** Not provided

Formulation/vehicle: Test article dissolved in distilled water

Methods:
Strains/species/cell line: *Salmonella typhimurium* TA 100, TA 1535, TA 98, and TA 1537, and *Escherichia coli* WP2*uvr*A
Dose selection criteria:

Basis of dose selection: Dose-range finding study, highest dose normally studied in laboratory (5 mg/plate)

Range finding studies: Toxicity test at concentrations of 0.15, 0.5, 1.5, 5.0, 15, 50, 150, 500, 1500, and 5000 mcg/plate, with incubation at 37°C for 48 hours. The results showed no toxicity in any strain tested at up to the highest concentration of 5000 mcg/plate. Therefore, 5000 mcg/plate, the highest dose normally studied in this assay, was chosen for the mutagenicity assay.

Test agent stability: Not provided

Metabolic activation system: S9 mix: microsome fraction derived from livers of Sprague-Dawley rats induced with phenobarbital and 5.6-benzoflavone

Controls:

Vehicle: Distilled water

Negative controls: Distilled water

Positive controls: The following positive controls were used:

S9 Mix	Tester Strain	Compound	Lot Number	Concentration (mcg/ml)
Absence	TA 100	N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG)	V1N4017	3
	TA 1535	ENNG	V1N4017	5
	WP2*uvr*A	ENNG	V1N4017	2
	TA 98	2-Nitrofluorene (2-NF)	V9E8930	1
	TA 1537	9-Aminoacridine (9-AA)	M7B4472	80
Presence	TA 100	2-Aminoanthracene (2-AAN)	V8P4045	1
	TA 1535	2-AAN	V8P4045	2
	WP2*uvr*A	2-AAN	V8P4045	20
	TA 98	2-AAN	V8P4045	0.5
	TA 1537	2-AAN	V8P4045	2

Comments: Positive controls were appropriate, tested in parallel with and without S9; Assay was conducted in triplicate, replicated 2X

Exposure conditions:

Incubation and sampling times: Incubation period 48 hours

Doses used in definitive study: 78, 156, 313, 625, 1250, 2500, and 5000 mcg/plate

Study design: Memantine HCl dissolved in water, 0.1 ml added to 2.0 ml top agar containing 0.05 mM L-histidine, biotin and L-tryptophan, 0.1 ml culture of tester strain, and 0.5 ml S9 mix or 0.1 M phosphate buffer, pH 7.4, and mixture poured onto 30 ml minimal glucose agar plates (3 plates/concentration) and solidified; plates were incubated 48 hours at 37°C; colonies were counted and plates examined for precipitation and background lawn growth of non-revertant *his* or *trp* bacteria.

Analysis:

No. of replicates: 2

Counting method: Not provided

Criteria for positive results: 2X increase in revertants compared to controls, increase dose-related and reproducible

Summary of individual study findings:

Study validity:

1. Test product and S9 sterility (no colony visible at 1/10 maximum concentration after incubation 48 hours at 37°C
2. Purity and stability of the test article, and counting method not provided
3. Strains and dose selection adequate

Study outcome:

The results of the dose finding study showed no bacteriostatic activity by the test article at up to 5000 mcg/plate. Therefore, 5000 mcg/plate was chosen to be the highest dose for the mutagenicity study. No dose-related and reproducible increase in number of revertants (number of colonies/plate) to 2X the control numbers were observed, in the presence and absence of metabolic activation with S9 mix. The numbers of revertants were increased by more than 2X over controls in all positive controls.

Study title: Gene Mutation Assay in Chinese Hamster V79 Cells In Vitro with Memantine-HCl

Key findings:

- Concentration-dependent increase in the number of mutant colonies per 10^6 cells in the presence of metabolic activation in Experiments I and II, up to 4.61X (Experiment I at the highest concentration of 300 mcg/ml) and 6.1X (Experiment II at the highest concentration of 300 mcg/ml)
- No increase in number of mutants in Experiments III and IV in the presence of metabolic activation at concentrations of up to 300 mcg/ml
- Results equivocal under the conditions of this study

Study no: 219510
Study type: Mutagenicity: to detect mutation (resistance to 6-thioguanine) at the HPRT locus in mammalian cells
Volume # 61, and page # 235
Conducting laboratory and location:

Date of study initiation: February 15, 1991
GLP compliance: yes (x) no ( )
QA reports: yes (x) no ( )
Drug Memantine HCl, **lot #** R 4338, **radiolabel** Not applicable, **and % purity** 100.58%

Formulation/vehicle: Test article dissolved in minimal essential medium (MEM)

Methods:

Strains/species/cell line: Chinese hamster V79 cell line

Dose selection criteria:

Basis of dose selection: Dose range-finding study (pre-test for toxicity)
Range finding studies: 100% cytotoxicity at concentrations of 300-2600 mcg/ml without metabolic activation, and at 1000-2600 mcg/ml with metabolic activation; in

the assay with metabolic activation, the concentration of 300 mcg/ml resulted in a mean number of colonies of 67 compared to 283.5 in the negative control, and a plating efficiency of 23.6%; No decrease in mean number of colonies and plating efficiency at concentrations of 1-100 mcg/ml compared to controls.

Test agent stability: Pure at least one year, in solvent 24 hours

Metabolic activation system: Hepatic microsomes obtained from livers of Wistar rats treated with Aroclor 1254 (S9)

Controls:

Vehicle: Minimal Essential Medium (MEM) solvent

Negative controls: Minimal Essential Medium (MEM)

Positive controls: Ethylmethanesulfonate (EMS,) in nutrient medium without metabolic activation, and 7,12-dimethylbenz(a)anthracene (DMBA,) in dimethylsulfoxide (DMSO) with metabolic activation

Comments: Appropriate controls used, dosing adequate based on results of the preliminary toxicity study

Exposure conditions:

Incubation and sampling times: Cells were exposed to test article, and negative and positive control articles for 4 hours

Doses used in definitive study: Experiment I and II: 3.0, 10.0, 30.0, and 100.0 mcg/ml without S9 and 10.0, 30.0, 100.0, and 300.0 mcg/ml with S9; Experiments III and IV: with S9 mix, 100, 200, 250, and 30 mcg/ml

Study design: After 4 hours exposure to test article, negative control, and positive control articles with and without S9 mix, or to S9 alone, the cells were subcultured in normal medium. Dose related plating efficiency was determined, and the cells were allowed phenotype expression of mutation.

The colonies with more than 50 cells were counted using a preparation microscope. Mutant frequencies were determined using the number of mutant colonies corrected for cell survival.

Analysis:

No. of replicates: 2X

Counting method: The colonies (>50 cells) were counted using a preparation microscope

Criteria for positive results: Significant (defined as 3X spontaneous increase), concentration-related increase in mutant frequency, or reproducible significant response for at least one test point

Summary of individual study findings:

Study validity:

1. Numbers of mutant colonies/10^6 cells in negative/solvent controls within laboratory historical control range (5-45 mutants/10^6 cells)
2. Significant increase in mutant colony frequencies by the positive control articles
3. Plating efficiency of negative/solvent controls > 50%

Study outcome: The results are presented in the following tables:

Results of the Mutagenicity Study in Chinese Hamster V79 Cells
Experiments I and II

Treatment	Concentration (mcg/ml)	S9	Experiment I		Experiment II	
			Mean # Mutant Colonies/Flask*	Mutant Colonies per 10^6 Cells	Mean # Mutant Colonies/Flask*	Mutant Colonies per 10^6 Cells
Negative Control	0	-	6 ± 1.9	14.5	2.0 ± 1.0	6.7
Positive Control (EMS)	1	-	108.0 ± 16.1	438.6	108.0 ± 10.9	457.2
Test Article	1	-	Culture not continued	Culture not continued	Culture not continued	Culture not continued
"	3	-	7.0 ± 4.6	21.9	7.4 ± 1.5	31.3
"	10	-	6.0 ± 2.0	14.8	8.6 ± 2.5	33.3
"	30	-	1.6 ± 1.1	5.2	4.6 ± 2.6	16.7
"	100	-	2.0 ± 0.7	8.6	13.2 ± 2.7	36.9
"	300	-	Severe toxic effects	Severe toxic effects	Severe toxic effects	Severe toxic effects
Negative Control	0	+	5.2 ± 2.6	15.2	1.8 ± 1.3	5.0
Negative Control w/DMSO	0	+	3.4 ± 2.1	7.4	4.6 ± 1.8	13.7
Positive Control with DMBA	15.4	+	184.4 ± 17.4	566.3	151 ± 17.6	713.2
Test Article	1	+	Culture not continued	Culture not continued	Culture not continued	Culture not continued
"	3	+	Culture not continued	Culture not continued	Culture not continued	Culture not continued
"	10	+	6.6 ± 1.7	17.9	2.4 ± 0.9	7.6
"	30	+	7.0 ± 1.4	17.2	2.6 ± 1.5	9.2
"	100	+	7.2 ± 4.5	17.7	4.6 ± 1.5	19.2
"	300	+	9.4 ± 3.0	34.1	14.6 ± 5.2	50.0

*Mean of 5 flasks, ± S.D.

Results of the Mutagenicity Study in Chinese Hamster V79 Cells
Experiments III and IV

Treatment	Concentration (mcg/ml)	S9	Experiment III		Experiment IV	
			Mean # Mutant Colonies/Flask*	Mutant Colonies per 10^6 Cells	Mean # Mutant Colonies/Flask*	Mutant Colonies per 10^6 Cells
Negative Control	0.00	+	5.4 ± 1.8	14.9	2.8 ± 0.8	9.3
Negative Control w/DMSO	0.00	+	19.4 ± 5.2	54.5	4.6 ± 2.6	16.5
Positive Control with DMBA	7.70	+	213 ± 12.0	1417	269 ± 8.3	972.2
Test Article	100	+	5.6 ± 0.9	17.8	8.2 ± 2.6	21.6
"	200	+	7.4 ± 1.1	22.1	6.8 ± 0.8	19.3
"	250	+	5.8 ± 1.5	16.3	7.8 ± 1.3	24.9
"	300	+	5.4 ± 2.7	15.8	4.4 ± 1.5	11.6

*Mean of 5 flasks, ± S.D.

No statistically significant increase in the number of mutants was observed in the cells treated with the solvent control (Minimal Essential Medium) or solvent control with DMSO. There was a concentration-dependent increase in mutation rate in experiments I

and II, at memantine HCl concentrations of 10, 30, 100, and 300 mcg/ml, in the presence of metabolic activation. In Experiment I, the number of mutant colonies per 10^6 cells at the highest concentration of 300 mcg/ml was 2.24X the number in the negative control flasks, and 4.61X the number of mutant cells in the negative control with DMSO flasks, in the presence of metabolic activation. In Experiment II, there was a significant increase in number of mutant colonies per 10^6 cells at the highest evaluable concentration (100 mcg/ml) only, of 5.5X the number in the negative controls, and no dose relationship was observed, in the absence of metabolic activation with S9 mix. However, in the presence of metabolic activation in Experiment II, there was a significant, dose-related increase in the number of mutant colonies per 10^6 cells, of up to 10.1X the number in the negative controls and 3.69X the number in the negative controls with DMSO, at the highest dose of 300 mcg/ml. No memantine-induced increases in mutant colonies were observed in Experiments III and IV at the concentrations of 100-300 mcg/ml in the presence of S9. Significant increases in number of mutations were observed in the positive control-treated flasks. The dosing was considered to be adequate due to excessive cytotoxicity at concentrations of 300 mcg/ml and higher. The sponsor concluded that the increase in mutation rates at the highest doses in the presence of metabolic activation were probably due to random effect (Experiment II), or that the mutation rate was within historical range of $5/10^6$ - $45/10^6$ cells (Experiment I), and therefore that memantine HCl was negative for point mutations at the HGPRT locus in V79 cells. Although memantine was negative in Experiments III and IV, conducted to prove the relevance of the results from the first 2 experiments, the mutagenic potential of memantine HCl cannot be ruled out because of the positive findings in Experiments I and II in the presence of S9 mix.

Study title: Chromosome Aberration Assay in Human Lymphocytes In Vitro with Memantine HCl

Key findings:

- No clastogenicity observed by *in vitro* metaphase analysis in human lymphocytes
- Testing parameters were adequate

Study no: 219521
Study type: Clastogenicity (chromosome aberrations) *in vitro* in human lymphocytes
Volume # 61, and page # 267
Conducting laboratory and location:

Date of study initiation: February 4, 1991
GLP compliance: yes (x) no ( )
QA reports: yes (x) no ( )
Drug Memantine HCl, **lot #** R4338, **radiolabel** Not applicable, **and % purity** 100.58%

Formulation/vehicle: Dulbecos Modified Essential Medium/HAM'S F12 Medium (DMEM/F12, without calf serum

Methods:

Strains/species/cell line: Human peripheral blood lymphocytes from a healthy male, age 37

Dose selection criteria:

Basis of dose selection: Preliminary cytotoxicity test

Range finding studies: Mitotic index determined at the following concentrations:

Without S9 mix: 24 hours: 0.003, 0.01, 0.03, 0.10, 0.30, 1.00, 1.50, 2.20 mg/ml
48 hours: 0.03, 0.10, 0.30, 1.00, 1.50, 2.20 mg/ml

With S9 mix: 24 hours: 0.003, 0.01, 0.03, 0.10, 0.30, 1.00, 1.50, 2.20 mg/ml
48 hours: 0.03, 0.10, 0.30, 1.00, 1.50, 2.20 mg/ml

The results showed a mitotic index of 0.0 at the concentrations of 0.30-2.20 mg/ml without S9 and at 0.30 (one vessel only, with a 50% reduction in MI in the other vessel) – 2.20 (both vessels) mg/ml with S9 mix at 24 hours, and at 0.30-2.20 mg/ml without S9 and 1.00-2.20 mg/ml with S9 with S9 mix at 48 hours. Therefore, the following concentrations were chosen for the main study: 0.01-0.10 mg/ml with and without S9 at 24 hours, 0.10 mg/ml without S9 at 48 hours, 0.30 mg/ml with S9 at 48 hours.

Test agent stability: Pure: at least one year; In solvent: 24 hours in water

Metabolic activation system: Aroclor 1254 induced rat microsomal enzymes (final protein concentration 0.75 mg/ml S9)

Controls:

Vehicle: 1:1 Dulbecos modified Essential medium/HAM's F12 Medium (DMEM/F12)

Negative controls: DMEM/F12

Positive controls: Ethylmethanesulfonate (EMS, 0.72 mg/ml [redacted] without S9), Cyclophosphamide (CPA, 60.0 mcg/ml, [redacted] with S9)

Comments: Controls acceptable

Exposure conditions:

Incubation and sampling times: The lymphocytes were incubated 48 hours at 37°C with 11% CO_2, and then treated with test article with and without S9 mix for 4 hours. Colcemide was added 3 hours before harvesting, to arrest the cells in metaphase. The cells were harvested at 24 and 48 hours after treatment, treated with hypotonic solution, centrifuged, fixed (methanol and glacial acetic acid), and suspension dropped onto clean microscope slides, stained with Giemsa, and analyzed.

Doses used in definitive study: 0.01-0.10 mg/ml with and without S9 at 24 hours, 0.10 mg/ml without S9 at 48 hours, 0.30 mg/ml with S9 at 48 hours

Study design:

Analysis: Isolated lymphocytes were induced to divide in culture by phytohaemagglutinin ([redacted] for 48 hours at 37°C with 11% CO_2, and then were exposed to control medium, memantine HCl, or positive control articles for 4 hours. Cell division was blocked during metaphase by colcemide (3 hours before harvesting), and the cells were fixed, smeared onto slides and stained. The chromosomes from 100 well spread metaphases per culture were examined microscopically for chromosome breaks, fragments, deletions, exchanges, chromosomal disintegrations, and gaps. The mitotic index (% cells in mitosis) was determined and the number of polyploid cells (% polyploid metaphases) was scored.

No. of replicates: 2X

Counting method: The breaks, fragments, deletions, exchanges, chromosomal disintegrations, and gaps were counted in at least 100 metaphases per culture using a [redacted] microscope with 100x oil emersion objectives.

Criteria for positive results: Statistically significant (chi-square test) increase in aberration rate with at least one concentration tested compared to control.

Summary of individual study findings:

Study validity:

1. Numbers of chromosomal aberrations in the negative control cultures within historical control data range for the laboratory.
2. Significant increase in frequencies of aberrations by the positive control articles.
3. Adequate controls used.
4. Incubation time with memantine appropriate.
5. Dosing with memantine appropriate.

Study outcome: There were no significant increases in chromosome breaks, fragments, deletions, exchanges, disintegrations, and gaps by memantine HCl at any concentration up to 0.1 mg/ml with and without metabolic activation with S9 for 24hours and without S9 for 48 hours, and at up to 0.3 mg/ml in the presence of S9 for 48 hours (aberration rates in the memantine-treated cells 0.00%-3.00% compared to 1.00%-2.50% in the negative controls). The positive control articles ethylmethanesulfonate and cyclophosphamide significantly increased the number of cells with structural chromosome aberrations (20% each), with and without metabolic activation. Therefore, in agreement with the sponsor's conclusion, memantine HCl was negative for clastogenicity at concentrations up to 0.1 (with and without S9 at 24 hours and without S9 at 48 hours) and 0.3 mg/ml (with S9 at 48 hours), under the conditions tested.

Study title: Metaphase Analysis on Memantine Hydrochloride

Key findings:

- Memantine HCl was negative for clastogenicity in the metaphase analysis assay in rat spermatocytes, under the conditions of this study.

Study no: PTX 12/82309
Study type: *In vivo*, clastogenicity, in mammalian spermatocytes
Volume # 61, and page # 306
Conducting laboratory and location:

Date of study initiation: January 29, 1982
GLP compliance: yes (x) no ( )
QA reports: yes (x) no ( )
Drug Memantine hydrochloride, **lot #** D145-charge Nr. 12-256, **radiolabel** not applicable, **and % purity** Not provided

Formulation/vehicle: Test article suspended in sterile distilled water

Methods:

Strains/species/cell line: Male CD rats of Sprague-Dawley origin (weights 40-45 g,

Dose selection criteria:

Basis of dose selection: Preliminary toxicity study
Range finding studies: In phase I, 4 male rats/dose were administered 2 doses of vehicle or memantine HCl at the doses of 100, 400, 800, 1200, 1600, and 2000 mg/kg/dose (0.1 ml/kg), 24 hours apart, by oral gavage. In phase II, 10 rats/group were administered 2 doses of vehicle or memantine HCl at the doses of 200, 400, and 600 mg/kg/dose (0.1 ml/kg), 24 hours apart, by oral gavage. The results for phase I showed 100% lethality at 600-2000 mg/kg. There were 1 and 2 deaths in the 100 and 400 mg/kg groups (n=4), respectively in phase I, and 4 deaths at 400 mg/kg (n=10) in phase II. The clinical signs were piloerection, lethargy, ptosis, and abnormal gait from 1-7 hours after the first dose at 100-200 mg/kg, from 1-24 hours after the first dose at 400-800 mg/kg, and from 1 hour until sacrifice at 6 hours after the second dose at 100-800 mg/kg. Based on these results, 300 mg/kg was selected for the high dose in the metaphase analysis.

Test agent stability: Not provided
Metabolic activation system: Not applicable
Controls:
Vehicle: Sterile distilled water
Negative controls: Sterile distilled water
Positive controls: Mitomycin C (4.0 mg/kg 24 hours apart, total dose 8 mg/kg, at 0.4 mg/ml.
Comments: Controls were appropriate
Exposure conditions:
Incubation and sampling times: 6 hours after the second of 2 doses, 24 hours apart.
Doses used in definitive study: 0, 37.5, 75.0, 150.0 mg/kg/dose, 2 doses 24 hours apart for a total dose of 0, 75, 150, and 300 mg/kg

Study design: Ten male rats per group were administered sterile water vehicle (0.1 ml/kg PO), memantine HCl (0.1 ml/kg PO) or Mitomycin C (0.1 ml/kg IP) in 2 doses (see under Doses Used in the Definitive Study, above), 24 hours apart. The rats were sacrificed by cervical dislocation at 6 hours after the second dose. The testes were removed, and tubules isolated and minced. After soaking in hypotonic solution for 30 minutes at room temperature and centrifugation, the cells were fixed (aceto-methanol), suspended, mounted on cold slides (2 slides/rat), stained (Giemsa), and examined. The incidence of chromosomal aberrations (chromatid gaps, breaks, translocations, and exchanges, dicentric chromosomes, acentric chromosomal fragments, minute chromosomal fragments, chromosome rings, and complete metaphase pulverisations) were determined in 50 metaphase cells per rat.

Analysis:
No. of replicates: 2 slides/rat
Counting method: Examination by light microscopy
Criteria for positive results: Statistically significant increase in aberrant metaphase counts (non-parametric equivalent of the method of least significant differences, Janckheere's distribution-free test, Spearman's correlation test) comparing cells from the test article and control vehicle treated rats

Summary of individual study findings:
Study validity:

1. Statistically significant increase in aberrant metaphase counts in the positive control groups compared to the controls
2. High dose (300 mg/kg PO) acceptable as maximum dose for this assay
3. Controls were appropriate
4. Study parameters (e.g., numbers of animals and dose groups)

Study outcome:

Mean Number of Aberrant Cells per 50 Metaphases

Treatment	Total Dose (mg/kg)	Number of Aberrant Cells per 50 Metaphases			
		Including Gaps		Excluding Gaps	
		Mean	Range	Mean	Range
Sterile Distilled Water	0	0.9		0.4	
Memantine HCl	75	1.0		0.5	
Memantine HCl	150	0.6		0.4	
Memantine HCl	300	1.2		0.7	
Mytomycin C	8	8.2		4.6	

No evidence of mutagenic potential, including chromatid gaps, breaks, translocations, and exchanges, dicentric chromosomes, acentric chromosomal fragments, minute chromosomal fragments, chromosome rings, and complete metaphase pulverisations, was observed in rat spermatocytes in the metaphase stage of cell division, under the conditions of this study. In agreement with the sponsor's conclusions, memantine HCl was negative in the metaphase analysis assay in rats.

Study title: Memantine HCl: Micronucleus Test

Key findings:

- Memantine HCl was negative for clastogenicity in the micronucleus test; no induction of micronuclei in polychromatic erythrocytes of bone marrow in mice were observed at up to 80 mg/kg IP on 2 consecutive days.

Study no: 5525-M-06496
Study type: *In vivo*, clastogenicity
Volume # 61, **and page #** 327
Conducting laboratory and location:

Date of study initiation: September 19, 1996
GLP compliance: yes (x) no ( )
QA reports: yes (x) no ( )
Drug Memantine HCl, **lot #** R7206, **radiolabel** Not applicable, **and % purity** 99.3%

Formulation/vehicle: Test article dissolved in sterile distilled water of injectable grade

Methods:

Strains/species/cell line: Male and female — CD-1 mice
weights 29-37 g males and 22-28 g females, ages 5-6 weeks)
Dose selection criteria:

Basis of dose selection: Preliminary toxicity study: see under Range finding studies, below

Range finding studies: Male and female mice were administered memantine HCl at doses of 20, 40, 60, and 80 mg/kg IP (10 ml/kg). The results showed mortality of 13/15 females and 2/15 males at 80 mg/kg, and no deaths at the lower doses. The treatment-related clinical signs were unconsciousness, lethargy, and respiratory difficulty at the high dose, and piloerection and increasing respiratory rate at the intermediate and lose doses. Based on the results of the range finding study, the dose of 80 mg/kg was chosen for the high dose in the main study.

Test agent stability: No precipitate reported

Metabolic activation system: Not applicable

Controls:

Vehicle: Sterile distilled water of injectable grade

Negative controls: Sterile distilled water of injectable grade

Positive controls: Mitomycin-C (0.2 ml/kg, 2 mg/kg)

Comments: Controls were appropriate

Exposure conditions:

Incubation and sampling times: See under Study design, below

Doses used in definitive study: 0, 20, 40, 80 mg/kg IP at 10 ml/kg

Study design: 5 mice/sex/group received vehicle control, memantine HCl, and mitomycin-C intraperitoneally, and additional groups of 5 mice/sex received vehicle control and the high dose of 80 mg/kg (total 10 mice/sex/group). 5 mice/sex/group were sacrificed by cervical dislocation at 24 hours after dosing, and the additional negative control and high dose mice were sacrificed by cervical dislocation at 48 hours after dosing. The femurs were isolated and ends removed, bone marrow was removed and bone marrow smears prepared and mounted on slides. The cells were stained with May-Gruenwald and Giemsa solutions, examined by light microscopy (16x) and scored for relative proportions of polychromatic erythrocytes (PCE) and normochromatic erythrocytes (NCE), ratio of PCE/NCE and frequency of micronucleated PCE/1000 (at 100x power). The results from the test and positive control mice were compared to those of the negative controls using a modified chi-squared calculation.

Analysis:

No. of replicates: 3 slides/mouse

Counting method: PCE/NCE ratios and micronucleus frequencies/1000 cells, then counting of micronuclei in PCE up to 1000 PCE

Criteria for positive results:

1. Statistically significant increase in frequency of micronucleated PCE in at least 1 dose group in at least 1 time point
2. Significant increase in frequency of micronucleated PCE exceeding historical vehicle control range
3. Evidence of increased (even if insignificant) frequencies of micronucleated PCE at other doses/time points, or dose response effect (even if insignificant)

Summary of individual study findings:

Study validity:

1. High dose (80 mg/kg) acceptable as maximum dose for this assay

2. Controls were appropriate
3. Acceptable PCE:NCE ratio observed
4. Incidence of micronucleated PCE in vehicle control groups within historical control range
5. Minimum 10 animals/group evaluated in the control and high dose groups
6. Significant increase in frequency of micronucleated PCE in the positive control group

Study outcome:

There were no statistically significant increases in the frequency of micronucleated PCE by memantine HCl at any dose (from 10-80 mg/kg IP) or timepoint (24 and 48 hours). The mean range of frequencies of micronucleated PCE in the treated groups was 0.8-1.3 at 24 hours and 1.2 at 48 hours, compared to 1.6 at 24 hours and 1.2 at 48 hours in the negative controls, and 43.4 in the positive control treated mice. Therefore, memantine tested negatively in the in vivo micronucleus test under the conditions tested in concurrence with the sponsor's conclusions.

Study title: Mutagenicity Study of MRZ 2/325 in the Salmonella Typhimurium Reverse Mutation Assay (In Vitro)

Key findings:

- The memantine metabolite, MRZ 2/325, was negative in the Ames test in 5 strains of Salmonella typhimurium including 4 strains that have GC pairs at the primary reversion site and 1 strain (TA 102) that detects cross-linking mutagens, at concentrations of 10-10000 mcg/plate, with and without metabolic activation with S9, under the conditions of this study

Study no: [redacted] 10551/97
Study type: Mutagenicity: to detect induction of DNA base pair substitution and frameshift mutations (Ames *et al.*, Mutation Res. 31:347-363, 1975)
Volume # 61, and page # 356
Conducting laboratory and location: [redacted]

Date of study initiation: June 23, 1997
GLP compliance: yes (x) no ( )
QA reports: yes (x) no ( )
Drug MRZ 1/325, **lot #** 10S-6166, **radiolabel** Not applicable, **and % purity** Not provided

Formulation/vehicle: Test article dissolved in ethanol

Methods:

Strains/species/cell line: Strains Studied in the Ames Test

Strain		Type of Mutation	Mutant Gene
S. typhimurium	TA 1535	Base-pair substitution	his G 46
S. typhimurium	TA1537	Frameshift	his C 3076
S. typhimurium	TA 102	Contains ochre mutation	his G 428
S. typhimurium	TA 98	Frameshift	his D 3052
S .typhimurium	TA 100	Base-pair substitution	his G 46

Dose selection criteria:

Basis of dose selection: Preliminary toxicity study

Range finding studies: The results of the range finding study, at concentrations up to 10000 mcg/plate MRZ 2/325 in strain TA 100 showed no cytotoxicity in the evaluation of background lawns and number of revertants. Therefore, although the maximum required concentration in the absence of cytotoxicity is 5000 mcg/plate, the high dose of 10000 mcg/plate was selected for the main study.

Test agent stability: No precipitate was reported in this study

Metabolic activation system: 5.0 ml 5% rat liver S9 (Aroclor 1254-induced, in water for injection) combined with $MgCl_2$ + KCl salt solution, glucose-6-phosphate, NADP, phosphate buffer and sterile water for injection.

Controls:

Vehicle: Ethanol (concentration not provided in this submission)

Negative controls: Ethanol (concentration not provided in this submission)

Positive controls: The following positive controls were used:

Without metabolic activation	
Sodium azide in H_2O (10 mcg/plate)	TA 1535, TA 100
2-nitro-9H-fluorene in DMSO (10 mcg/plate)	TA 98
9-amino-acridine in ethanol (100 mcg/plate)	TA 1537
Methyl methane sulfonate MMS in DMSO (1300 mcg/plate)	TA 102
With metabolic activation	
2-anthraceneamide in DMSO (2 mcg/plate)	TA 98, TA 100, TA 102, TA 1535, TA 1537

All positive control articles were obtained from [redacted].

Comments: Controls were appropriate

Exposure conditions:

Incubation and sampling times: 48 hours at 37°C

Doses used in definitive study: 10.0, 31.6, 100, 316, 1000, 3160, and 10000 mcg/plate

Study design: MRZ 2/325 dissolved in ethanol, was added to molten agar (100 ml, 45°C) with histidine (10 ml 0.5 mM) and biotin (10 ml 0.5mM), with and without S9 mix, and test organisms (0.1 ml suspension at 10^8-10^9 cells/ml). The cultures were poured into Petri dishes on solidified agar layers at 3 plates per concentration of MRZ 2/325 per strain, and were incubated at 37°C for 48 hours, and the number of revertant colonies were determined.

Analysis:

No. of replicates: 2

Counting method: Not described in this submission

Criteria for positive results:

1. Significant increase in number of revertants compared to solvent control
2. At least 2X increase in number of revertants for TA 98, TA 100 and TA 102 compared to controls, and 3X increase for TA 1535 and TA 1537 compared to controls
3. Significant dose-related effect
4. Positive results reproducible
5. Histidine independence of revertants confirmed (streaking of random samples on histidine-free agar plates)

Summary of individual study findings:

Study validity:

1. Confirmation of tester strain genotypes for histidine and biotin requirement, rfa deep rough character, and ampicillin resistance
2. Reversion frequencies for negative controls within range of spontaneous reversion frequency for the laboratory (TA 98: 20-60; TA 100: 100-200; TA 102: 240-320; TA 1535: 10-35; and TA 1537: 3-20)
3. Statistically significant increase in number of revertants in the positive control treated cultures
4. Test product sterility (no colony visible at highest dose after incubation 48 hours at 37°C)
5. Dose selection adequate

Study outcome: No increases in number of revertants/plate were observed at any concentration of MRZ 2/325 tested (from 10-10000 mcg/plate) compared to control frequencies, with or without metabolic activation with S9 in any *S. typhimurium* strain tested. In agreement with the sponsor's conclusion, the memantine metabolite, MRZ 2/325, was negative in the Ames test, under the conditions of this study.

VI. CARCINOGENICITY:

Study titles: The following studies are reviewed in this section:

Long-Term Feeding Study of Memantine HCl in B6C3F1 Mice – Carcinogenicity Study (— Study 7279/92, Vol. 38, p. 1)

Pathology Working Group Report, — , Study 488-003, Vol. 37, p. 250)

Evaluation of the Lymphoma Histopathologic Diagnosis in the Mouse Carcinogenicity Study with Memantine (—432005, Vol. 37A, p. 1)

Statistical Report of Mouse Survival and Neoplastic Lesions (— No. 6277-146 (mouse), Vol 37C, p. 492)

Key study findings:

- No evidence of carcinogenic potential by memantine HCl at doses of up to 40 mg/kg/day in the diet (10X the MRHD of 20 mg in a 60 kg patient on a BSA basis) for 113 weeks in B6C3F1 mice, under the conditions of this study
- Study validity: Adequate number of animals, dose selection, survival, parameters evaluated and duration of treatment were used, stability and homogeneity of memantine in the animal diet was demonstrated, and drug absorption was verified in blood samples, similar metabolism of memantine in mice and humans demonstrated in separate studies

Study number: — 7279/92, — 488, 003, —432005, and — 6277-146
Volume # 37 page 250, Volumes 37A-C, and Volumes 38-45

Conducting laboratory and location: ——

Date of study initiation: February 18, 1993
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug Memantine HCl, **lot #** R 7206, **and % purity** 99.7%
CAC concurrence: No. The sponsor submitted the protocols for the mouse and rat carcinogenicity studies for review in 1992. Comments were conveyed to the sponsor by Dr. Robert Osterberg, Acting Assistant Director for Pharmacology/Toxicology, ODE, CDER (letter dated August 27, 1992).

Study Type: Lifetime administration (approximately 2-year bioassay): 113 weeks
Species/strain: B6C3F1 Mice
Number/sex/group; age at start of study: 50/sex/group; ages 4 weeks (males) and 5 weeks (females)
Animal housing: The mice were housed singly in — cages in a temperature controlled (22°C ± 3°C) and humidity controlled (60% ±20%) room with 12 hour light/dark cycle. The mice were fed — diet and provided tap water for drinking, *ad libitum.*
Formulation/vehicle: Test article mixed with food
Drug stability/homogeneity: Drug substance stable until September 1996. Stability of test substance in diet analyzed for 3 areas (top, mid, bottom) of food bucket at 13-week intervals, for all dose levels.

Methods:

Doses: 0 (diet only, 2 groups each for males and females), 2.5, 10.0 and 40.0 mg/kg/day; The concentrations of memantine HCl in the diet were adjusted weekly according to food consumption in the previous weeks.

Basis of dose selection: The doses were selected based on the results of a 13-week preliminary study on oral toxicity in B6C3F1 CrlBR mice (n=10/sex/dose), at doses of 5, 20, 80, 160, and 320 mg/kg/day in the diet. The results showed reduced body weight gain at 80, 160, and 320 mg/kg/day when compared to controls, that was more pronounced in the males (10%, 14% and 21% lower that control gain, respectively, at 80, 160, and 320 mg/kg/day) than in the females (6%, 11%, 12%, respectively). Decreased food consumption (16.3%-29.3%), decreased relative and absolute liver (males and females), spleen (males and females) and heart (females only) weights, increased relative kidney weights (males), changes in corneal epithelium (3/10 females), and vacuolation of the tubular epithelium in the kidney (1 female) were observed at the dose of 160 mg/kg/day. The dose of 320 mg/kg/day was lethal for the male mice.

Restriction paradigm for dietary restriction studies: — — diet provided *ad libitum*, fasted overnight before necropsy. Tap water for drinking via drinking bottles, changed daily, *ad libitum.*
Route of administration: Oral by admixture in the diet
Frequency of drug administration: Continuous in diet
Dual controls employed: Yes, both negative controls were untreated powdered diet
Interim sacrifices: None
Satellite PK or special study group(s): None

Deviations from original study protocol: None

Statistical methods: For the statistical analyses, all of the parameters in the treated mice were compared to those in Control group 1. The Multiple t-test (Dunnett, 1955) was used for evaluation of the results for body weights, food consumption, hematology, organ weights, IgG and IgM levels and bone marrow. The Exact test (Fisher) was used to evaluate survival rate and histopathology results. The test for positive trend (Peto *et al.*, 1980) was used for neoplastic microscopic findings. Statistical significance was defined as $p<0.05$ for rare findings, and $p<0.01$ for common lesions.

The results were re-analyzed in 2002 by [redacted] if there were no significant differences between the control groups, they were combined for analysis (Control 1 + Control 2 vs treated); if the control groups were significantly different, the analyses were conducted separately (Control 1 vs treated, Control 2 vs treated); occult tumors were analyzed by asymptotic interval-based test for incidence >8, or interval-based exact permutation test if not, both asymptotic and exact tests using PROC MULTTEST in SAS. Cox-Tarone binary regression method was used for palpable tumors using palpation time as onset time. Benign and malignant tumors were analyzed individually and combined. Positive trends were evaluated at the 0.005 and 0.025 levels and negative trends and pair-wise group comparisons at the 5.0% significance level, for common and rare (<1% incidence) tumors. Control groups were combined in the analyses except for ovarian benign granulosa tumors (controls shown significantly different).

Observations and times:

Clinical signs: Daily
Mortality: Twice daily
Palpable masses (> 5mm, persisting >2 weeks): Weekly from week 27 to end of study
Body weights: Baseline (Weeks –2 and –1), weekly up to Week 13, then every 2 weeks from Week 14 to the end of the study
Food consumption: Weekly until week 13, Biweekly from Week 14 to the end of the study
Water consumption: Daily
Examination of eyes: Weeks 26, 52, 78, and 102, using ophthalmoscope and slit-lamp, included cornea and anterior chamber
Auditory function: Noise test (response to finger-snapping sound), weekly throughout study
Hematology: Blood samples from the retrobulbar venous plexus under ether anesthesia in Week 112
Clinical chemistry: The antibodies IgG and IgM only: at study termination
Bone Marrow: Femoral bone, 3 smears/animal, at study termination
Organ weights: Adrenals, brain, epididymides, heart, kidneys, liver, lung, lymph node (submaxillaris), ovaries, pituitary, spleen, testes, uterus, thyroid, thymus, and tumors
Gross pathology: Adrenals, aorta, bone (*os femoris*), bone marrow (*os femoris*), brain (*in toto*), cecum, costochondral junction (rib), ears (external and internal), epididymides, eyes (with optic nerve), gall bladder, Harderian glands, heart, intestine (colon, rectum, duodenum, jejunum, ileum), kidneys, liver, lungs (with mainstem bronchi), lymph nodes (cervical, mesenteric, submaxillaris), macroscopically visible lesions, mammary gland, mesovarium/mesometrium, muscle (skeletal, leg), nasal cavity (including pharynx), nerve (sciatic), nose, esophagus, ovary, pancreas, pituitary, prostate, salivary gland, seminal

vesicle, skin (left flank), spinal cord, spleen, sternum, stomach, teeth (incisors, molars), testicles, thymus, thyroid (including parathyroids), tongue (including base), trachea (including larynx), tumors and conspicuous regional lymph nodes, urinary bladder, uterus (including cervix), and vagina

Histopathology: Adrenals, aorta *abdominalis*, bone (*os femoris*), bone marrow (*os femoris*), brain, cecum, costochondral junction (rib), ears (external and internal), epididymides, eyes (with optic nerve), gall bladder, Harderian glands, heart, intestine (colon, rectum, duodenum, jejunum, ileum), kidneys, larynx, liver, lungs (with mainstem bronchi), lymph nodes (cervical, mesenteric, submaxillaris), mammary gland, mesovarium/mesometrium, muscle (skeletal, leg), nasal cavity (including pharynx), nerve (sciatic), esophagus, ovary, pancreas, pituitary, prostate, salivary gland, seminal vesicle, skin (left flank), spinal cord, spleen, sternum, stomach, testicles, thymus, thyroid (including parathyroids), tongue (including base), trachea, tumors and conspicuous regional lymph nodes, urinary bladder, uterus (including cervix), and vagina

Toxicokinetics: Plasma memantine analyzed in 0.2 ml blood samples at study termination

Results:

Mortality: No treatment-related effects. The survival rates are presented in the following table:

Survival Rates and Survival Times in Mice Administered Memantine HCl In the Diet, Daily for 113 Weeks

Group	Dose (mg/kg/day)	Survival Rate To Week 113 (%)		Mean Survival Time (Weeks)			
				Prematurely Deceased/Sacrificed		Terminal Sacrificed	
		Males	Females	Males	Females	Males	Females
1	Control 1	84	78	96.1	96.2	110.3	109.3
2	Control 2	84	70	81.3	101.0	107.9	109.4
3	2.5	80	70	105.5	91.9	111.5	106.7
4	10.0	80	72	94.2	89.5	109.2	106.4
5	40.0	84	70	96.3	103.4	110.3	110.1

The histopathology examination in the premature deaths showed the following microscopic effects (selected to present effects with apparent increase in the memantine-treated mice, however no differences from Control 1 group were statistically significant):

Microscopic Findings in the Premature Deaths and Premature Sacrifices (Percent incidence)

	Memantine Dose (mg/kg/d, males)					Memantine Dose (mg/kg/d, females)				
	C1 n=8	C2 n=8	2.5 n=10	10 n=10	40 n=8	C1 n=11	C2 n=15	2.5 n=15	10 n=14	40 n=15
Brain: lympho-histioc. Infiltration	0	0	10	0	13	-	-	-	-	-
Brain: mineralization	25	38	20	30	38	64	40	27	14	33
Rib: fibrosis of cartilage	13	13	20	20	38	9	7	0	15	20
Eyes: autolysis	25	38	30	30	63	18	27	60	36	60
Gall bladder: autolysis	0	25	30	20	50	18	27	27	57	20
Genital: lymphocytic	0	0	33	0	100	-	-	-	-	-

infiltration										
Harderian gland: lympho-histioc. infiltration	13	0	40	10	25	9	0	0	0	7
Harderian gland: glandular ectasia	0	0	0	10	13	-	-	-	-	-
Kidney: lympho-histioc. infiltration	25	25	50	40	38	0	0	27	21	7
Kidney:suppurative nephritis/pyelitis	-	-	-	-	-	0	0	0	0	13
Liver: hepatocyte vacuolation	0	0	20	10	25	18	0	0	29	20
Liver: necrosis	25	13	30	10	63	9	20	13	21	33
Mammary gland: lympho-histioc. infiltration	0	0	0	0	25	0	0	7	0	0
Ovaries: cyst	-	-	-	-	-	9	20	7	38	33

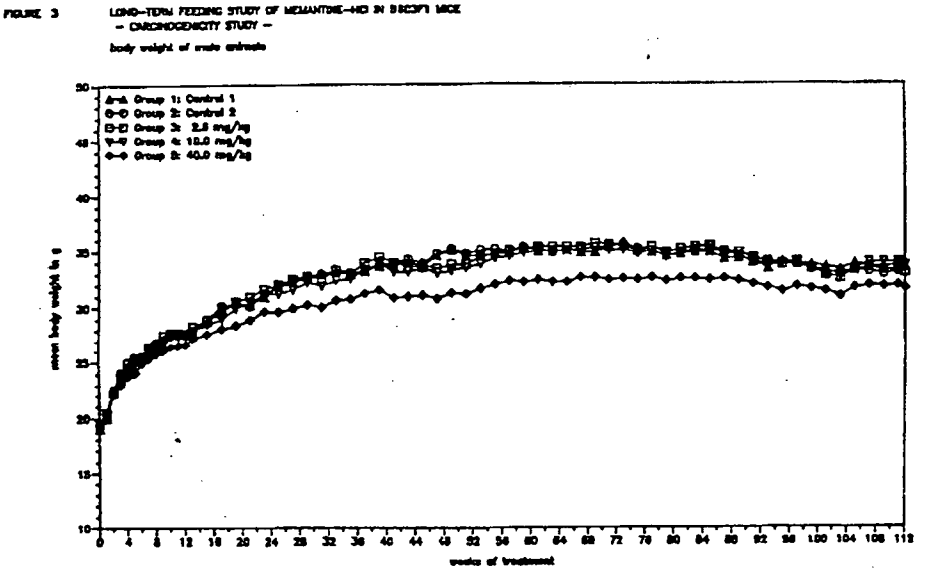
Clinical signs: Dyspnea in the high dose females (moderate, 10%-16% incidence compared to 10% in the controls, from week 87-end of study)
Palpable masses (> 5mm, persisting >2 weeks): No treatment-related effects on latency to development of palpable tumors; the incidence and latency period of the palpable masses are presented in the following table:

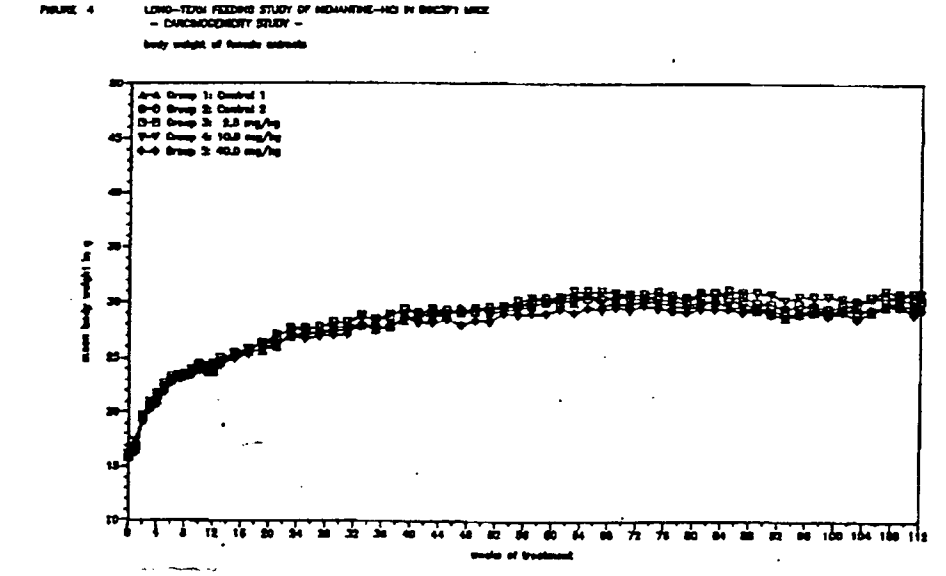
Palpable Masses in Mice Administered Dietary Memantine HCl Daily for 113 Weeks (values represent animal number, latency in weeks presented in parentheses)

Tumor Type	Organ	Control 1	Control 2	2.5 mg/kg/d	10 mg/kg/d	40 mg/kg/d
Males						
Cystadenoma	Eye					420 (99)
Hepatocellular carcinoma	Abdominal cavity			248 (98) 242 (99)	320 (73)	439 (89)
Lipoma	Genital region					413 (63)
Lymphoma	Genital region	23 (82) 46 (85) 15 (99) 49 (106)	52 (63) 96 (98) 82 (110)	238 (86)	327 (65) 324 (99)	407 (106)
	Abdominal	22 (106)	64 (66) 99 (92)			430 (106)
	Mammary			201 (106)	339 (24)	
Lymphoma Pleomorphic type	Mammary gland					402 (106)
Sebaceous adenoma	Mammary gland					416 (68)
Females						
Hepatocellular carcinoma						484 (93)
Lymphoma	Abdominal	122 (101)	200 (102)	256 (93) 285 (102) 267 (103) 297 (110)	361 (66) 356 (89)	451 (95) 454 (101)
	Mammary	122 (101)	158 (93)		375 (93)	
	Genital	141 (111)			380 (93)	
	Neck				361 (66)	
	Axillary				380 (93)	

Squamous cell carcinoma	Axillary (skin)			261 (107)		
	Genital					479 (89)
	Mammary gland			275 (73)		

Body weights: The mean body weights are presented in the following figures:





In the male mice, mean body weights were significantly lower than the Group 1 controls at 10 mg/kg/day in Treatment Weeks 47 and 49, and at 40 mg/kg/day in Treatment Weeks 3 through 112. At the end of the study, the mean body weight in the high dose males (31.6 g) was 6% lower than in the Group 1 controls (33.5 g). In the female mice, the mean body weights were significantly lower than controls at 10 mg/kg/day in Week 91, and at 40 mg/kg/day in Weeks 4 and 47. There were no differences in mean bodyweights between the treated and control female mice at the end of the study.

Food consumption: No treatment-related effects
Water consumption: No treatment-related effects
Examination of eyes: No treatment-related effects
Auditory function: No treatment-related effects
Hematology: No treatment-related effects
Clinical chemistry: No treatment-related effects
Bone Marrow: No treatment-related effects
Organ weights: No treatment-related effects, excluding abnormal tissue enlargements and other changes
Gross pathology: No treatment-related effects
Histopathology:

Non-neoplastic: Organs with increased non-neoplastic findings in male and/or female memantine-treated mice are shown in the following table:

Mice affected (Combined Decedents and Terminals, Percent incidence, n=50/sex/group)

	Memantine Dose (mg/kg/d, males)					Memantine Dose (mg/kg/d, females)				
	C1	C2	2.5	10	40	C1	C2	2.5	10	40
Adrenal: nodular hyper-plasia	2	0	2	0	14	0	2	0	0	2
Rib: fibrosis of cartilage	10	34**	14	14	32**	8	6	6	4	6
necrosis of cartilage	12	26	34**	24	0*	8	6	0	0	2
fibrosis of marrow	0	0	10	0	0	0	4	2	4	10*
Harderian gland: ectasia	8	0	2	2	14*	0	0	0	0	2
Kidney: lympho-histioc. infiltration	14	10	28	22	32*	4	0	14	8	10
Lymph node (submax.): brown pigment	0	7	2	15*	11*	5	4	9	2	5
Lung:lympho-histioc. infiltration	2	0	10	0	4	0	2	0	0	10*
Urinary bladder:lymphoc. follic. hyperplasia	10	10	24	10	14	2	4	4	2	16*

*Significantly different from control ($p<0.05$); **significantly different from control ($p<0.01$)

Neoplastic: No statistically significant increases in neoplastic lesions in the memantine-treated mice compared to the Control 1 mice. A summary of the total tumor incidence for benign and malignant tumors is presented in the following table:

Neoplasm Summary in Mice Administered Memantine in the Diet for 113 Weeks (Values Represent Incidence, Percent Incidence in Parentheses)

	Memantine Dose (mg/kg/d, males)					Memantine Dose (mg/kg/d, females)				
	C1	C2	2.5	10	40	C1	C2	2.5	10	40
All Mice Combined										
Total Mice/Group	50	50	50	50	50	50	50	50	50	50
Total Primary Tumors	101 (202)	96 (192)	84 (168)	91 (182)	70 (140)	85 (170)	85 (170)	85 (170)	90 (180)	77 (154)
Total Mice with Tumors	50 (100)	50 (100)	48 (96)	50 (100)	46 (92)	50 (100)	49 (98)	50 (100)	50 (100)	49 (98)
Total Mice with Multiple Tumors	34 (68)	32 (64)	27 (54)	29 (58)	21 (42)*	27 (54)	28 (56)	26 (52)	30 (60)	25 (50)
Total Benign	39 (38)	33 (34)	31 (36)	28 (30)	22 (31)	23 (27)	28 (32)	20 (23)	30 (33)	20 (25)
Total Malignant	62 (61)	63 (65)	53 (63)	63 (69)	48 (68)	62 (72)	57 (67)	65 (76)	60 (66)	57 (74)
Total Malignant with Metastasis	48 (77)	52 (82)	44 (83)	50 (79)	42 (87)	51 (82)	51 (89)	53 (81)	54 (90)	49 (85)
Terminal Sacrifice										
Total Mice/Group	42	42	40	40	42	39	35	35	36	35
Total Primary Tumors	88 (209)	82 (195)	67 (167)	72 (180)	54 (128)	65 (166)	57 (162)	62 (177)	67 (186)	54 (154)
Total Mice with Tumors	42 (100)	42 (100)	39 (97)	40 (100)	38 (90)	39 (100)	34 (97)	35 (100)	36 (100)	35 (100)
Total Mice with Multiple Tumors	30 (71)	28 (66)	21 (52)	22 (55)	15 (35)	21 (53)	18 (51)	20 (57)	22 (61)	16 (45)
Total Benign	37 (42)	28 (34)	25 (37)	23 (31)	15 (27)	17 (26)	21 (36)	17 (27)	26 (38)	15 (27)
Total Malignant	51 (57)	54 (65)	42 (62)	49 (68)	39 (72)	48 (73)	36 (63)	45 (72)	41 (61)	39 (72)
Total Malignant with Metastasis	39 (76)	45 (83)	35 (83)	40 (81)	35 (89)	40 (83)	34 (94)	37 (82)	38 (92)	35 (89)
Premature Death/Sacrifice										
Total Mice/Group	8	8	10	10	8	11	15	15	14	15
Total Primary Tumors	13 (162)	14 (175)	17 (170)	19 (190)	16 (200)	20 (181)	28 (186)	23 (153)	23 (164)	23 (153)
Total Mice with Tumors	8 (100)	8 (100)	9 (90)	10 (100)	8 (100)	11 (100)	15 (100)	15 (100)	14 (100)	14 (93)
Total Mice with Multiple Tumors	4 (50)	4 (50)	6 (60)	7 (70)	6 (75)	6 (54)	10 (66)	6 (40)	8 (57)	9 (60)
Total Benign	2 (15)	5 (35)	6 (35)	5 (26)	7 (43)	6 (30)	7 (25)	3 (13)	4 (17)	5 (21)
Total Malignant	11 (84)	9 (64)	11 (64)	14 (73)	9 (56)	14 (70)	21 (75)	20 (86)	19 (82)	18 (78)
Total Malignant with Metastasis	9 (81)	7 (77)	9 (81)	10 (71)	7 (77)	11 (78)	17 (80)	16 (80)	16 (84)	14 (77)

*Significantly different from Control 1 ($p<0.05$)

There were no treatment-related increases in the incidence of neoplastic lesions in the memantine-treated mice when compared to controls, that were outside the range of historical control incidence (National Toxicology Program (NTP), National Cancer Institute, >400 long term carcinogenicity studies in male and female B6C3F1 mice, Haseman *et al.*, Neoplasm Incidences in B6C3F1 Mice: NTP Historical Data). Re-examination of the microscopic slides by the Pathology Working Group (PWG)

conducted after inconsistencies were detected in the original final report, confirmed the original conclusion that no treatment-related increase in the incidence of neoplastic lesions indicating carcinogenic potential by memantine were present.

A second re-evaluation by (see Amendment to Pending NDA dated September 3, 2002, Study Report 6277-146) showed no positive trends for common and rare tumors. There were significant negative trends for adrenocortical adenoma and bronchial-alveolar adenoma in the lungs in the male mice, and malignant pleomorphic lymphoma in the hematopoietic system and pituitary combined adenoma/adenocarcinoma in the female mice. Additionally, there were significant treatment-related decreases in the incidence of pituitary adenoma, combined malignant lymphocytic/pleomorphic lymphoma in the hematopoietic system in the females. Histiocytic sarcoma in the hematopoietic system was increased at the low dose only, and liver hepatocellular adenoma was increased at the high dose when compared to Control Group 2 but not to Control Group 1 in the females.

The incidence of malignant lymphomas, diagnosed at a high incidence in the original study, was re-evaluated with the following differences noted (reproduced from the original NDA submission):

Incidence (%) of Malignant Lymphoma in B6C3F1 Mice

	Males					Females				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Study Pathologist	88%	98%	78%	96%	82%	98%	98%	100%	100%	96%
PWG	16%	18%	4%	16%	12%	36%	36%	26%	36%	18%
NTP*	8.3% (2-20%)					20.9% (6%-42%)				

*Historical control incidence; Range in parentheses, n=1355 male and 1353 female mice

The microscopic slides for all tissues were re-evaluated by a consultant pathologist (Study 432005) to resolve the differences between the original study pathologist diagnoses and those of the Pathology Working Group with regard to the incidence of malignant lymphoma. The results of the third evaluation for lymphoid neoplasms by are presented in the following table (reproduced from the original NDA submission):

Incidence of Lymphoma and Hematopoietic Neoplasms in B6C3F1 Mice (n=50/sex/group)

	Males					Females				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Lymphoma (pleomorphic)	5 (10%)	5 (10%)	3 (6%)	7 (14%)	5 (10%)	14 (28%)	18 (36%)	10 (20%)	15 (30%)	7 (14%)
Lymphoma (lymphocytic)	2 (4%)	2 (4%)	0 (0%)	1 (2%)	0 (0%)	3 (6%)	1 (2%)	1 (2%)	2 (4%)	2 (4%)
All Lymphomas	7 (14%)	7 (14%)	3 (6%)	8 (16%)	5 (10%)	17 (34%)	19 (38%)	11 (22%)	17 (34%)	9 (18%)
Histiocytic Sarcoma	1 (2%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (8%)	0 (0%)	0 (0%)
Granulocytic Leukemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
All Neoplasms	8 (16%)	8 (16%)	4 (8%)	8 (16%)	5 (10%)	17 (34%)	19 (38%)	16 (32%)	17 (18%)	9 (18%)

There were no treatment-related effects in the incidence of lymphomas and hematopoietic neoplasms, except for increased histiocytic sarcoma at the low dose in the female mice, that was also higher than in the historical controls. This finding was considered to be incidental because there were no observations of histiocytic sarcoma at the mid-dose and high dose in either sex. The results of the third evaluation by —— concurred with those reported in the second examination (Pathology Working Group).

Toxicokinetics: The plasma memantine levels at the end of the study are presented in the following table (reproduced from the original NDA submission):

Plasma Memantine Levels in Mice Treated (Dietary) for 113 Weeks

Dose (mg/kg/day)	Sex	Mean Plasma Memantine (ng/ml)
0	Males	<5
	Females	<5
2.5	Males	17.3
	Females	7.4
10	Males	60.9
	Females	52.1
40	Males	260.9
	Females	175.0

MOUSE MTD/HUMAN MRD: Not determined in this study
MOUSE/HUMAN BSA RATIO: (40mg/kg/d)(3)/(20mg/60kg/d)(37) = 120/12.333 = 10X
MOUSE/HUMAN AUC RATIO: Not determined in this study

*No correction for protein binding: unknown in mice

Summary of individual study findings:
Adequacy of the carcinogenicity study and appropriateness of the test model: The carcinogenicity study in mice used an adequate number of animals, and showed adequate survival, parameters evaluated and duration of treatment. The dose selection was based on the results of a 13-week preliminary study on oral toxicity in B6C3F1 mice showing reduced body weight gain at 80 mg/kg/day when compared to controls, that was more pronounced in the males (10% lower than control gain) than in the females (6% lower than control gain). Additionally, in the carcinogenicity study, the high dose of 40 mg/kg/day was associated with significantly decreased body weights throughout the study in the males, dyspnea in the high dose females, significantly increased rib cartilage fibrosis, kidney lympho-histiocytic infiltration, and lymph node brown pigment in the males, and rib marrow fibrosis, lympho-histiocytic infiltration in the lung, nephritis, liver necrosis, and lymphocytic follicular hyperplasia in the urinary bladder in the females. In a safety pharmacology study in mice (Irwin test), memantine HCl at doses of 30 mg/kg and higher produced adverse CNS effects including decreased awareness from 30-150 minutes after dosing, indicated by decreased ability to place self after being put in different positions and decreased righting reflex. Prior concurrence of the protocol was implied by letter conveyed to the Sponsor after Agency review (letter dated August 27, 1992). The high dose used in the carcinogenicity study was within 1/4-1/2 the MTD in the 13-week range finding study, and represented 10X the MRHD on a BSA basis. Memantine produced no carcinogenic signal in the rats and mice of either sex, and produce significant negative trends for several neoplastic lesions in both species. The sponsor demonstrated stability and homogeneity of

memantine in the animal diet and drug absorption was verified in blood samples. Based on these factors, the high dose of 40 mg/kg/day in the carcinogenicity study in mice is probably adequate.

Previous studies showed that memantine is metabolized by oxidation of the amino functional group (1-nitro-deaminated 7-hydroxy memantine and regio-isomers, 1-nitroso-deaminated memantine), with nitrosated and nitrated metabolites at or below 4.2% of the renally excreted memantine compounds (unchanged memantine excreted 68.8%). In comparison, memantine is excreted nearly completely (>90%) unchanged in the urine in humans. The remaining 10% memantine is excreted as N-gludantan conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine.

The relative concentrations of memantine metabolites are presented in the following table:

Urine Memantine and Memantine Metabolite Concentrations (mcg/ml) in Mouse, Rat and Human*

Memantine/Metabolite	Isomers	Mouse	Rat	Human
Memantine	-	319.08	330.00	2.90
Memantine N-gludantan conjugate	-	4.24	61.35	0.55
6-Hydroxy Memantine	Cis-	6.56	101.20	0.25
	Trans-	8.83	36.10	0.26
1-Nitroso-deaminated Memantine		9.36	1.64	0.38

*Doses administered: 80 mg/kg/day for 5 days in mouse (8-hour period after last dose), 80 mg/kg in rat (8 hours after dose), and 3X5mg over 19 days in humans (urine collected over 24 hours on days19/20)

Evaluation of tumor findings: The sponsor originally concluded that there was no difference between memantine-treated and control mice in the incidence and type of neoplastic lesions, and no evidence of carcinogenic potential by memantine HCl at doses of up to 40 mg/kg/day in mice. However, the sponsor noted inconsistencies in the tumor data set during preparation of the electronic database, and requested peer review and conduction of a Pathology Working Group (PWG). The microscopic slides were re-examined by the 6-member PWG at [redacted] which supported the conclusion in the original evaluation that there was no evidence of carcinogenic potential by memantine HCl under the conditions of this study. A third evaluation was conducted by a consultant pathologist at [redacted] (Study [redacted] 432005) to resolve the differences between the original study pathologist diagnoses and those of the Pathology Working Group with regard to the incidence of malignant lymphoma. The results of the microscopic examination by [redacted] concurred with those of the PWG, showing no treatment-related effects on the incidence of lymphomas and hematopoietic neoplasms in the male and female mice. In conclusion, there was no evidence of carcinogenic potential by dietary memantine HCl at doses of up to 40 mg/kg/day for 113 weeks in B6C3F1 mice, under the conditions of this study. The high dose represented approximately 10X the MRHD of 20 mg in a 60 kg patient on a BSA basis (AUC data not available).

The results of the carcinogenicity studies in mice were presented to the Executive CAC committee on July 22, 2003. The committee agreed that the doses for the male mice were adequate based on toxicity in the high-dose group (body weight changes in the males) and agreed

that although a MTD was no reached in the female mice, the high dose was within 1/-1/2 of an MTD, and considering adequate doses were used in the rats and male mice, and no increases in tumors were seen in these studies, the mouse study is acceptable. The Committee agreed that there were no drug-related increases in tumors.

Study title: The following studies are reviewed in this section:

Long-Term Feeding Study of Memantine HCl in Sprague-Dawley Rats – Carcinogenicity Study, — Study 7280/92, Vol. 46, p. 1

Histopathology Peer Review and Pathology Working Group Review of a Long-term Feeding Study of Memantine-HCl in Sprague-Dawley Rats: Amended Pathology Working Group Report, ——— Study 488-002, Vol. 45a, p. 1

Statistical Report of Rat Survival and Neoplastic Lesions. —— Study 6277-146 (rat), Vol. 45a, p. 137.

Long-Term Feeding Study of Memantine-HCl in Sprague-Dawley Rats – Carcinogenicity Study. Histopathology of the Kidneys. — Study 7280a/92, Vol. 55, p. 1

Key study findings:

- No evidence of carcinogenic potential by memantine HCl at doses of up to 40 mg/kg/day in the diet (reduced to 20 mg/kg/day from Weeks 71-128/129, 19X the MRHD of 20 mg in a 60 kg patient on a BSA basis) for 128-129 weeks in Sprague Dawley rats, under the conditions of this study
- Study validity: Adequate number of animals, dose selection, survival, parameters evaluated and duration of treatment were used, stability and homogeneity of memantine in the animal diet was demonstrated, and drug absorption was verified in blood samples, similar metabolism of memantine in rats and humans demonstrated in separate studies

Study number: 7280/92
Volumes # 46-55 **and page #** 1, and **Volume** 45a, **page #** 1
Conducting laboratory and location: ———

———

Date of study initiation: September 3, 1992
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug Memantine HCl, **lot #** R 7206, **and % purity** 99.7%
CAC concurrence: No. The sponsor submitted the protocols for the mouse and rat carcinogenicity studies for review in 1992. Comments and concurrence were conveyed to the sponsor by Dr. Robert Osterberg, Acting Assistant Director for Pharmacology/Toxicology, ODE, CDER (Letter dated August 27, 1992, attached at the end of the Carcinogenicity Section of this Review).

Study Type: Lifetime administration (approximately 2-year bioassay): 129 weeks
Species/strain: — rat: — , SD, ———

Number/sex/group; age at start of study: 50/sex/dose / Ages 4 weeks
Animal housing: The rats were housed singly [redacted] cages in a temperature controlled (22°C ± 3°C) and humidity controlled (60% ± 20%) room with 12 hour light/dark cycle. The rats were fed [redacted] diet and provided tap water for drinking, *ad libitum.*
Formulation/vehicle: Test article mixed with food
Drug stability/homogeneity: Drug substance stable until September 1996. Stability of test substance in diet analyzed for 3 areas (top, mid, bottom) of food bucket at 13-week intervals, for all dose levels.

Methods:

Doses: 0 (diet alone, 2 groups), 2.5, 10.0, and 40.0 mg/kg/day (reduced to 20 mg/kg/day in test week 71 upon observations of kidney lesions and resulting marked increases in memantine blood concentrations with increasing toxicity, including body weight loss and dyspnea)
Basis of dose selection: The doses were selected based on the results of previous chronic toxicity studies in Sprague-Dawley rats by the sponsor. Memantine HCl administered by esophageal intubation at doses of 3-30 mg/kg/day for 8 weeks resulted in a dose-related reduction in body weight gain that was statistically significant at the high dose in the male rats (19% over week 1-8), and at 15 (11%, weeks 1-8) and 30 (17%, weeks 1-8) mg/kg/day in the female rats. The NOAEL was 3 mg/kg/day (1.5X the MRHD of 20 mg/d in a 60 kg patient on a BSA basis). The MTD was 15 mg/kg/day in the male rats (7X the MRHD) and <15 mg/kg/day in the female rats based on significantly reduced body weight gain and increases in adrenal, brain and gonad weights.

In a 13-week dose range-finding study, body weights were significantly reduced (8%, 20%, 33%, and 25% at 40, 90, 135, and 200 mg/kg/day, respectively, in the males, and 7%, 17%, 34%, and 18% at 30, 75, 120, and 180 mg/kg/day, respectively, in the females) compared to controls. Decreased proteins (7% in males at 40 mg/kg/day) and globulins (-10% in males at 40 mg/kg/day and females at 30 mg/kg/day), and increased serum alkaline phosphatase (33% at 30 mg/kg/day in the females) were observed, with values outside the range of historical control values. The urinalysis showed treatment-related increased ketones in the males at doses of ≥ 40 mg/kg/day.

The results of a 6-month toxicity study in Sprague-Dawley rats showed treatment-related reduction in mean body weights at 20 and 40 mg/kg/day in males (7% and 12%, respectively) and females (9% and 11%, respectively). There was a dose-related reduction of body weight gain by 12% and 21% in the males at 20 and 40 mg/kg/day, respectively, and by 17%, 23%, and 26% in the females at 10, 20 and 40 mg/kg/day, respectively. There was an increase in glucose (8%-19% at 40 mg/kg/day in the males and females on Days 22 and 183), alkaline phosphatase (15%-23% at 20 and 40 mg/kg/day in the males on days 92 and 183), A/G ratio (8%-30% at 20 and 40 mg/kg/day in the males on days 183 and 211), phosphorus (8%-21% at 20 and 40 mg/kg/day in the males and females on days 92 and 183), and decreased creatinine (8% at 40 mg/kg/day in the males on days 183 and 211).

Restriction paradigm for dietary restriction studies: None
Route of administration: Oral, in the diet

Frequency of drug administration: Continuous
Dual controls employed: Yes
Interim sacrifices: None
Satellite PK or special study group(s): None

Statistical methods: For the statistical analyses, all of the parameters in the treated rats were compared to those in Control group 1. The Multiple t-test (Dunnett, 1955) was used for evaluation of the results for body weights, food consumption, hematology, organ weights, IgG and IgM levels, bone marrow, and latency period of tumors. The Exact test (Fisher) was used to evaluate survival rate and histopathology results. The test for positive trend (Peto *et al.*, 1980) was used for neoplastic microscopic findings. Statistical significance was defined as $p<0.05$ for rare findings, and $p<0.01$ for common lesions.

The results were re-analyzed in 2002 by — The results were re-analyzed in 2002 by — if there were no significant differences between the control groups, they were combined for analysis (Control 1 + Control 2 vs treated); if the control groups were significantly different, the analyses were conducted separately (Control 1 vs treated, Control 2 vs treated). Occult tumors were analyzed by asymptotic interval-based test for incidence >8, or interval-based exact permutation test if not, both asymptotic and exact tests using PROC MULTTEST in SAS. Cox-Tarone binary regression method used for palpable tumors using palpation time as onset time. Benign and malignant tumors were analyzed individually and combined. Positive trends were evaluated at 0.005 and 0.025 levels and negative trends and pair-wise group comparisons at 5.0% significance level, for common and rare (<1% incidence) tumors. Control groups were combined in the analyses except for ovarian benign granulosa tumors (controls shown significantly different).

Observations and times:

Clinical signs: Daily
Mortality: Twice Daily
Palpable masses (>5 mm, persisting > 2 weeks): Weekly from Week 27 through study termination
Body weights: Weeks –2, -1, and weekly during dosing through week 13, then every 2 weeks until study termination
Food consumption: Weekly through Week 13, then biweekly until study termination
Water consumption: Daily
Ophthalmoscopy: Weeks 26, 52, 78, and 128, using an ophthalmoscope and slit-lamp, included cornea and anterior chamber
Auditory function: response to finger snapping sound, weekly throughout study
Hematology: Blood samples from the retrobulbar venous plexus under ether anesthesia in Week 128
Clinical chemistry: IgG and IgM
Bone Marrow: Femoral bone, 3 smears/animal, at study termination
Organ weights: Adrenals, brain, epididymides, heart, kidneys, liver, lung, lymph node (submaxillaris), ovaries, pancreas, pituitary, prostate, seminal vesicle, spleen, testes, uterus, thyroid, thymus, and tumors
Gross pathology: Adrenals, aorta, bone (os femoris), bone marrow (os femoris), brain (in toto), cecum, costochondral junction (rib), ears (external and internal), epididymides, eyes (with optic nerve), Harderian glands, heart, intestine (colon, rectum, duodenum,

jejunum, ileum), kidneys, liver, lungs (with mainstem bronchi), lymph nodes (cervical, mesenteric, submaxillaris), macroscopically visible lesions, mammary gland, mesovarium/mesometrium, muscle (skeletal, leg), nasal cavity (including pharynx), nerve (sciatic), nose, esophagus, ovary, pancreas, pituitary, prostate, salivary gland, seminal vesicle, skin (left flank), spinal cord, spleen, sternum, stomach, teeth (incisors, molars), testicles, thymus, thyroid (including parathyroids), tongue (including base), trachea (including larynx), tumors and conspicuous regional lymph nodes, urinary bladder, uterus (including cervix), and vagina

Histopathology: Adrenals, aorta abdominalis, bone (os femoris), bone marrow (os femoris), brain, cecum, costochondral junction (rib), ears (external and internal), epididymides, eyes (with optic nerve), Harderian glands, heart, intestine (colon, rectum, duodenum, jejunum, ileum), kidneys, larynx, liver, lungs (with mainstem bronchi), lymph nodes (cervical, mesenteric, submaxillaris), mammary gland, mesovarium/mesometrium, muscle (skeletal, leg), nasal cavity (including pharynx), nerve (sciatic), nose, esophagus, ovary, pancreas, pituitary, prostate, salivary gland, seminal vesicle, skin (left flank), spinal cord, spleen, sternum, stomach, testicles, thymus, thyroid (including parathyroids), tongue (including base), trachea, gross lesions, tumors and conspicuous regional lymph nodes, urinary bladder, uterus (including cervix), and vagina.

A separate, detailed histopathology examination of the kidneys was conducted by — (Study 7280a/92), based on the necropsy results in the main carcinogenicity study. Additionally, a histopathology peer review and Pathology Working Group were conducted (— Project 488-002) to examine all microscopic slides to evaluate the consistency of the diagnoses and the accuracy of the terminology used to classify the proliferative lesions in the original carcinogenicity study.

Toxicokinetics: Plasma memantine analyzed in 0.2 ml blood samples at study termination

Results:

Mortality: No treatment-related effects on survival rate and survival time

Survival Rates and Survival Times in Rats Administered Memantine HCl In the Diet, Daily for 128-129 Weeks

Group	Dose (mg/kg/day)	Survival Rate (%) to Week 129 / Week 128		Mean Survival Time (Weeks)			
				Prematurely Deceased/Sacrificed		Including Terminal Sacrificed	
		Males	Females	Males	Females	Males	Females
1	Control 1	34	26	108.1	102.6	115.2	109.2
2	Control 2	26	18	103.8	103.5	110.4	107.9
3	2.5	20*	26	103.0	102.2	108.2	108.9
4	10.0	34	30	101.3	99.3	110.7	107.9
5	40.0/20[a]	38	34	110.1	100.7	117.3	110.0

*Significantly different from Control 1, $p<0.05$

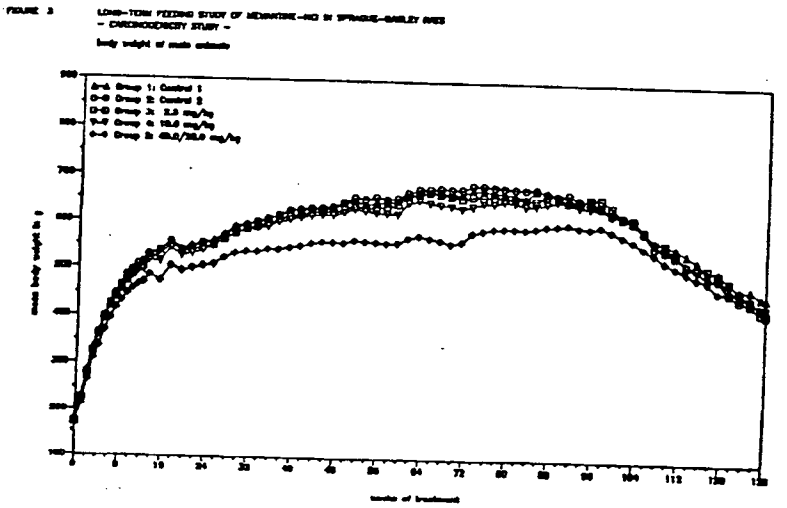
[a]Daily dose reduced from 40 mg/kg/day to 20 mg/kg/day from Week 71 through the end of the study, due to severely reduced body weights compared to controls

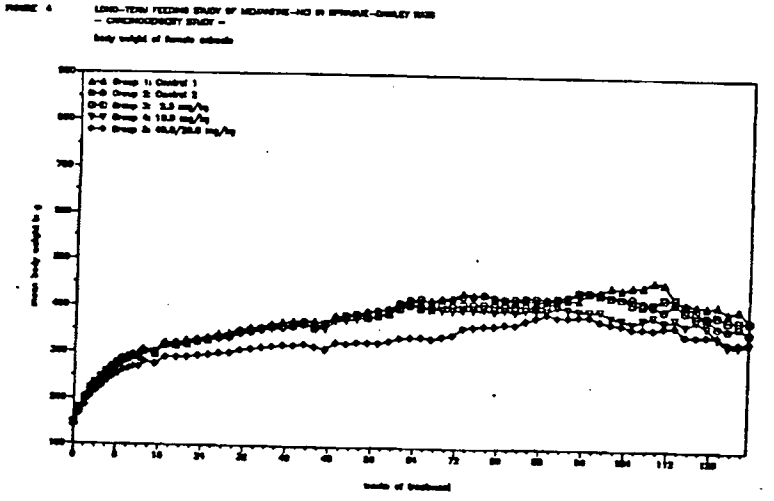
Clinical signs: Increased incidence and severity of dyspnea at 40 mg/kg/day from week 66 to week 71 and 20 mg/kg/day from week 71-129 in the males (20% incidence) and at

40 mg/kg/day from week 52 to week 71 and 20 mg/kg/day from week 71 to week 128 in the females (30% incidence), compared to controls (10-15% incidence)

Palpable masses: No treatment-related effects on latency to development of palpable tumors

Body weights: The mean body weights are presented in the following figures:





Mean body weights were reduced 9%-19% in the female rats at 10 mg/kg/day from week 97 to the end of the study, 16% and 19% in the male and female rats, respectively, at 40 mg/kg/day (up to week 71), and 11% and 7%-22% in the males (weeks 71-95) and females (weeks 71-end of study), respectively, at 20 mg/kg/day (reduction of high dose from week 71-end of study), when compared to controls (Group 1)

Food consumption: Increased food consumption in the mid-dose females during weeks 15-47, 69-85, and 125, and in the high-dose males (weeks 4, 8, 1, 15-23, and 71-93) and females (weeks 1-11, 15-19, and 39-125), compared to controls.

Water consumption: No treatment-related effects

Test substance intake: The mean test compound intake was 2.22-2.51, 8.85-10.03, 35.85-39.18, and 20.21 mg/kg/day at 2.5, 10, 40, and 20 mg/kg/day, respectively, in the male rats, and 2.32-2.50, 9.26-10.06, 37.59, and 20.35 mg/kg/day at 2.5, 10, 40, and 20 mg/kg/day, respectively, in the female rats throughout the study

Examination of eyes: No treatment-related effects

Auditory function: No treatment-related effects

Hematology: No treatment-related effects

Clinical chemistry: No treatment-related effects

Bone Marrow: No treatment-related effects

Organ weights: No treatment-related effects

Gross pathology: No treatment-related effects

Histopathology:

Non-neoplastic: Non-neoplastic findings that were increased in male and/or female memantine-treated rats compared to controls are shown in the following table:

Rats affected (Combined Decedents and Terminals, Percent incidence, n=50/sex/group)

	Memantine Dose (mg/kg/d, males)					Memantine Dose (mg/kg/d, females)				
	C1	**C2**	**2.5**	**10**	**40/20**	**C1**	**C2**	**2.5**	**10**	**40/20**
Kidney: medulla mineralization	8 (16%)	10 (20%)	7 (14%)	5 (10%)	40** (80%)	10 (20%)	8 (16%)	9 (18%)	13 (26%)	20* (40%)
Kidney: brown pigment	11 (22%)	10 (20%)	10 (20%)	16 (32%)	11 (22%)	1 (2%)	6 (12%)	9** (18%)	7* (14%)	4 (8%)
Lung: foamy macrophages	15 (30%)	15 (30%)	20 (40%)	21 (42%)	30** (60%)	24 (48%)	28 (56%)	25 (50%)	28 (56%)	38** (76%)
Lymph node: follicul. Hyperplasia (cervical)	7 (14%)	4 (8%)	9 (18%)	1 (2%)	2 (4%)	2 (4%)	3 (6%)	5 (10%)	3 (6%)	8* (16%)
Pituitary: hemorrhagic cyst	2 (4%)	5 (11%)	6 (12%)	9* (19%)	4 (8%)	5 (10%)	3 (6%)	1 (2%)	8 (16%)	2 (4%)
Spleen: brown pigment, red pulp	32 (64%)	30 (60%)	43** (86%)	38 (76%)	36 (72%)	34 (68%)	22 (44%)	31 (62%)	35 (70%)	28 (56%)
Testes: giant cells	2 (4%)	2 (4%)	1 (2%)	2 (4%)	8* (16%)	-	-	-	-	-
Tongue: lympho-histioc. infiltration	2 (4%)	2 (4%)	1 (2%)	1 (2%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	9** (18%)	3 (6%)
Uterus: cystic glandular hyperplasia	-	-	-	-	-	3 (6%)	6 (12%)	8 (16%)	9 (18%)	11* (22%)

*Significantly different from control 1 ($p<0.05$); **significantly different from control 1 ($p<0.01$)

A detailed histopathology examination of the kidneys, conducted by ~~ (Study 7280a/92), showed a statistically significant increase in renal medulla mineralization (mild to marked in the lumen and epithelium of the collecting tubules, also called dystrophic mineralization), at the high dose in the male and female rats. Non-treatment-related renal cortex and pelvic region

calcification, and chronic progressive nephropathy were found at a similar incidence and severity in all groups including the controls, although the severity of chronic nephropathy was greater in the males than in the females. The incidence and severity of mineralization in the medulla of the kidney are presented in the following tables:

Mineralization of the Medulla in the kidney (# rats affected/# rats examined)

Fate	Control 1		Control 2		2.5 mg/kg/day		10 mg/kg/day		40/20 mg/kg/day	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Terminal Sacrifice	5/17	2/13	4/13	3/9	2/10	4/13	1/17	6/15	16/19[bd]	8/17
Premature death/sacrifice	3/33	8/37	6/37	5/41	5/40	5/37	4/33	7/35	24/31[bd]	12/22[c]
All	8/50	10/50	10/50	8/50	7/50	9/50	5/50	14/50	40/50[bd]	20/50[ad]

[a]Significantly different from Control 1 ($p<0.05$)
[b]Significantly different from Control 1 ($p<0.01$)
[c]Significantly different from Control 2 ($p<0.05$)
[d]Significantly different from Control 2 ($p<0.01$)

Mean Severity Score for Mineralization of the Medulla in the Kidney

Fate	Control 1		Control 2		2.5 mg/kg/day		10 mg/kg/day		40/20 mg/kg/day	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
All	0.13	0.23	0.21	0.11	0.19	0.25	0.08	0.16	2.28	0.50

Neoplastic: No statistically significant increase in neoplastic lesions in the memantine-treated rats compared to the Control 1 rats. A summary of the total tumor incidence for benign and malignant tumors is presented in the following table:

Neoplasm Summary in Rats Administered Memantine in the Diet for 128-129 Weeks (Values Represent Incidence, Percent Incidence in Parentheses)

	Memantine Dose (mg/kg/d, males)					Memantine Dose (mg/kg/d, females)				
	C1	C2	2.5	10	40/20	C1	C2	2.5	10	40/20
All Rats Combined										
Total Rats/Group	50	50	50	50	50	50	50	50	50	50
Total Primary Tumors	109 (218)	103 (206)	77 (154)	94 (188)	83 (166)	129 (258)	135 (270)	119 (238)	120 (240)	122 (244)
Total Rats with Tumors	48 (96)	43 (86)	43 (86)	41 (82)	47 (94)	49 (98)	50 (100)	50 (100)	50 (100)	49 (98)
Total Rats with Multiple Tumors	34 (68)	33 (66)	24 (48)	28 (56)	23 (46)	38 (76)	40 (80)	35 (70)	43 (86)	41 (82)
Total Benign[a]	82 (75)	82 (79)	61 (79)	71 (75)	63 (75)	102 (79)	107 (79)	96 (80)	92 (76)	94 (77)
Total Malignant[a]	27 (24)	21 (20)	16 (20)	23 (24)	20 (24)	27 (20)	28 (20)	23 (19)	28 (23)	28 (22)
Total Malignant with Metastasis[b]	7 (25)	11 (52)	6 (37)	8 (34)	11 (55)	7 (25)	9 (32)	7 (30)	12 (42)	9 (32)
Terminal Sacrifice										
Total Rats/Group	17	13	10	17	19	13	9	13	15	17
Total Primary Tumors	40 (235)	33 (253)	11 (110)	31 (182)	25 (131)	43 (330)	35 (388)	39 (300)	45 (300)	49 (288)
Total Rats with Tumors	16 (94)	12 (92)	8 (80)	15 (88)	16 (84)	13 (100)	9 (100)	13 (100)	15 (100)	17 (100)
Total Rats with Multiple Tumors	12 (70)	11 (84)	3 (30)	11 (64)	6 (31)	12 (92)	8 (88)	12 (92)	15 (100)	17 (100)
Total Benign[a]	29 (72)	31 (93)	11 (100)	28 (83)	20 (80)	36 (83)	29 (82)	32 (82)	37 (82)	35 (71)

Total Malignant[a]	11 (27)	2 (6)	1 (0)	5 (16)	5 (20)	7 (16)	6 (17)	7 (17)	8 (17)	14 (28)
Total Malignant with Metastasis[b]	1 (9)	0 (0)	0 (0)	1 (20)	3 (60)	2 (28)	1 (16)	0 (0)	3 (37)	2 (14)
Premature Death/Sacrifice										
Total Rats/Group	33	37	40	33	31	37	41	37	35	33
Total Primary Tumors	69 (209)	70 (189)	66 (165)	63 (190)	58 (187)	86 (232)	100 (243)	80 (216)	75 (214)	73 (221)
Total Rats with Tumors	32 (96)	31 (83)	35 (87)	26 (78)	31 (100)	36 (97)	41 (100)	37 (100)	35 (100)	32 (96)
Total Rats with Multiple Tumors	22 (66)	22 (59)	21 (52)	17 (51)	17 (54)	26 (70)	32 (78)	23 (62)	28 (80)	24 (72)
Total Benign[a]	53 (76)	51 (72)	50 (75)	45 (71)	43 (74)	66 (76)	78 (78)	64 (80)	55 (73)	59 (80)
Total Malignant[a]	16 (23)	19 (27)	16 (24)	18 (28)	15 (25)	20 (23)	22 (22)	16 (20)	20 (26)	14 (19)
Total Malignant with Metastasis[b]	6 (37)	11 (57)	6 (37)	7 (38)	8 (53)	5 (25)	8 (36)	7 (43)	9 (45)	7 (50)

*Significantly different from Control 1 ($p<0.05$)
[a]Percentage value is Total Benign or malignant Tumors divided by the Total Primary Tumors
[b]Percentage value is Total Metastasized Tumors divided by the Total Malignant Tumors

No treatment-related increases in neoplastic lesions were identified in any tissue or organ, in the male and female rats, by the histopathology peer review (Pathology Working Group, — 488-002). The findings by the peer review group at — confirmed the original diagnoses and the accuracy of the terminology used to classify the proliferative lesions in the original carcinogenicity study.

Re-evaluation by — (see Amendment to Pending NDA dated September 3, 2002, Study Report 6277-146) showed no significant positive trends in either common or rare tumors. There were significant negative trends for pancreas islet adenocarcinoma and pancreas islet adenoma with adenocarcinoma, thyroid follicular adenoma/adenocarcinoma, benign pheochromocytoma in the adrenals, thyroid c-cell adenoma, and fibroma (all organs) in the males. Thyroid c-cell carcinoma was significantly increased at the mid-dose but not at the high dose. In the female rats, there was a significant negative trend for benign mammary fibroadenoma/adenoma and combined mammary fibroadenoma/adenoma/adenocarcinoma. Ovarian benign and benign/malignant granulosa cell tumors were increased at the mid-dose but not at the high dose in the females.

A detailed histopathology examination of the kidneys, conducted by — (Study 7280a/92), showed no increase in the incidence of neoplastic lesions, nor differences in type of neoplastic lesions in the kidney in memantine-treated rats when compared to the controls.

Toxicokinetics: Plasma memantine levels were higher in the females (mean 230 ng/ml) than in the males (mean 129 ng/ml) at the end of the study. The plasma memantine levels at the end of the study are presented in the following table:

Plasma Memantine Levels in Rats Treated (Dietary) for 128-129 Weeks

Dose (mg/kg/day)	Sex	Mean Plasma Memantine (ng/ml, range in

		parentheses)
0	Males	<5
	Females	<5
2.5	Males	18.6
	Females	11.8
10	Males	82.8
	Females	87.5
20	Males	129.2
	Females	230.1

RAT MTD/HUMAN MRD: Not determined in this study
RAT/HUMAN BSA RATIO: (40mg/kg/d)(6)/(20mg/60kg/d)(37) = 240/12.333 = 19X
Reduced to 20 mg/kg/day, Week 71-end of study: (20)(6)/(20/60)(37) = 10X
RAT/HUMAN AUC RATIO: Not determined in this study
*No correction for protein binding: unknown in rats

Summary of individual study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model: The carcinogenicity study in rats used an adequate number of animals, and showed adequate survival, parameters evaluated and duration of treatment. The sponsor demonstrated stability and homogeneity of memantine in the animal chow and drug absorption was verified in blood samples. The doses were acceptable, based on the results of previous chronic toxicity studies in Sprague-Dawley rats by the sponsor and on the toxicology evaluations in the present study. The high dose tested (40 mg/kg/day reduced to 20 mg/kg/day dietary in Week 71, 19X reduced to 10X the MRHD of 20 mg in a 60 kg patient on a BSA basis, AUC data not available) was at the MTD based on decreased body weights, increased incidence and severity of dyspnea, and non-neoplastic findings, including kidney mineralization and foamy macrophages in the lung.

Previous studies showed that memantine is metabolized by oxidation of the amino functional group (1-nitro-deaminated 7-hydroxy memantine and regio-isomers, 1-nitroso-deaminated memantine), with nitrosated and nitrated metabolites at or below 4.2% or the renally excreted memantine compounds (unchanged memantine excreted 68.8%). In comparison, memantine is excreted nearly completely (>90%) unchanged in the urine in humans. The remaining 10% memantine is excreted as N-gludantan conjugate, 6-hudroxy memantine, and 1-nitroso-deaminated memantine.

The relative concentrations of memantine metabolites are presented in the following table:

Urine Memantine and Memantine Metabolite Concentrations (mcg/ml) in Mouse, Rat and Human*

Memantine/Metabolite	Isomers	Mouse	Rat	Human
Memantine	-	319.08	330.00	2.90
Memantine N-gludantan conjugate	-	4.24	61.35	0.55
6-Hydroxy Memantine	Cis-	6.56	101.20	0.25
	Trans-	8.83	36.10	0.26
1-Nitroso-deaminated Memantine		9.36	1.64	0.38

*Doses administered: 80 mg/kg/day for 5 days in mouse (8-hour period after last dose), 80 mg/kg in rat (8 hours after dose), and 3X5mg over 19 days in humans (urine collected over 24 hours on days19/20)

Evaluation of tumor findings: No significant treatment-related increases in neoplastic effects were observed, under the conditions of this study. The sponsor originally concluded that there was no difference between memantine-treated and control rats in the incidence and type of neoplastic lesions, and no evidence of carcinogenic potential by memantine HCl at doses of up to 40 mg/kg/day (reduced to 20 mg/kg/day in Week 71) in rats. The microscopic slides were re-examined by the 6-member Pathology Working Group (PWG) at — — and by — which supported the original conclusion.

The results of the carcinogenicity study in rats were presented to the Executive CAC committee on July 22, 2003. The committee agreed that the doses used in the rat study were adequate, and that the study was negative for carcinogenicity.