

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-487

Pharmacology Review(s)

Drug class: N-methyl-D-aspartate (NMDA) receptor antagonist

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

Clinical formulation: Immediate release film-coated capsule-shaped tablets with the following composition (mg/tablet):

Ingredient (Core)	5.00 mg Tablet	10 mg Tablet	15 mg Tablet	20 mg Tablet
Memantine HCl	5.00	10.00	15.00	20.00
Lactose Monohydrate, NF				
Microcrystalline Cellulose, NF				
Colloidal Silicon Dioxide, NF				
Talc, USP				
Magnesium Stearate, NF				
Subtotal Weight (mg)				
Ingredients (Film Coat)				
Total Weight (mg)	128.75	257.5	388.1	515.0

Route of administration: Oral

Proposed use: Treatment of moderate to severe dementia of the Alzheimer's type, with a starting dose of 5 mg once daily, increased in 5 mg increments weekly, to 10 mg/day, 15 mg/day or 20 mg/day

Disclaimer: Tabular and graphical information is from the sponsor's submission unless stated otherwise.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

NDA 21-487 is approvable from a preclinical perspective.

B. Recommendation for Nonclinical Studies

No additional nonclinical studies are needed at this time.

C. Recommendations on Labeling:

The following changes to the CLINICAL PHARMACOLOGY Mechanism of Action section of the Label are recommended:

Mechanism of Action:

1

DRAFT LABELING

1

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

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

Orally administered memantine HCl is rapidly and completely absorbed, and shows extensive tissue distribution in animals, crosses the blood brain barrier and placenta, and binds to melanin. Metabolism is by hydroxylation, N-oxidation and conjugation, and the metabolic profiles are similar in mice, rats, baboons, and humans. Memantine is nearly completely excreted as parent drug and conjugated metabolites in the urine, within 48 hours in rodents, rabbits, dogs, pigs and baboons.

The acute oral toxicity of memantine was low in animals, with LD₅₀ values of approximately 500 mg/kg in rodents and 50 mg/kg in dogs, and included ataxia, tremor, bradypnea, dyspnea, muscular hypotonia, and convulsions at very high doses. In the safety pharmacology studies, memantine at high doses had notable CNS effects, including CNS excitation, decreased indices of awareness and motor activity, and interference with posture, muscle tone, reflexes and autonomic function. Memantine slightly reduced blood pressure in dogs and inhibited gastrointestinal activity in rodents. Subchronic and chronic high dose memantine was associated with CNS effects, reduced body weight gain and food consumption, and toxicity in the kidney and eyes. The no-effect doses for these effects were high, indicating a large safety margin for clinical use.

Memantine was not mutagenic in the Ames test, human lymphocytes, rats spermatocytes and in the mouse micronucleus test; the results were equivocal in Chinese Hamster V79 cells. No evidence of carcinogenic potential was found in 2-year feeding studies in mice and rats. Memantine had no adverse effects on male and female fertility and reproductive performance in rats, teratogenicity in rats and rabbits, and perinatal or postnatal development in rats (aside from slight decreases in pup weight and increased incidence of non-ossified cervical vertebrae). In special toxicology evaluations, ocular toxicity was indicated by cataract formation in pigmented but not in albino rats. Memantine induced vacuolation and necrosis in multipolar and pyramidal cells in the cortical layers III and IV of the cingulate and retrosplenial neocortices of rodents at very high multiples of the maximum recommended human dose (MRHD); the NOEL in rats was 6X the MRHD. No evidence of neuronal vacuolation and necrosis was found in baboons at doses up to 2X the MRHD on an AUC basis; however interpretation of the study is limited because concurrent controls were not evaluated and the retrosplenial cortices were not examined.

B. Pharmacologic Activity

Memantine demonstrated activity in animals related to the proposed indication in experimental paradigms of neuroprotection and memory enhancement, such as reduction of neuronal loss and cytoskeletal alterations in the hippocampus, immunoreactivity for astroglial and microglial macrophage markers GFAP and ED1, and apoptotic profiles in the hippocampus, and enhancement of long-term potentiation, spatial orientation, and memory acquisition.

C. Nonclinical Safety Issues Relevant to Clinical Use

The main target organs of toxicity in the animal toxicology studies were the CNS, eyes, and kidneys. The treatment-related CNS effects in rodents, decreased indices of awareness, mood, and motor activity, CNS excitation, and interference with posture, muscle tone, reflexes and autonomic function at high doses, and hyperactivity, staggering, aggressiveness, tremors, ptosis, huddled posture, piloerection, and hypothermia at extremely high doses in several species, suggest a potential for interference with cognitive, autonomic and motor functions in clinical use. The clinical safety data included reports of minor dose-related CNS effects including dizziness and confusion. Additionally, memantine HCl induced vacuolation and necrosis in the cingulate and retrosplenial cortices in rats. Although no memantine-related vacuolation and necrosis were observed in the cingulate cortices in baboons, and the risk of the NMDA-receptor antagonist-induced neuronal lesions to humans is unknown, the potential for neuronal toxicity in humans by memantine HCl cannot be ruled out. Patients given this drug should be adequately informed of the potential for neuronal damage suggested by the results of the studies in rodents.

Ocular toxicity by memantine at high doses in the animal studies included retinal blood vessel loss, endothelial vacuolation and pyknosis of the corneal epithelium, edema of the substantia propria and epithelium with thickening of Descemet's membrane, corneal edema and increased thickness, lens lesions, abnormal lysosomal storage in ganglion cells and retinal pigment epithelial cells, and focal eye opacities in the rodents, and opal turbidity of the cornea in the dogs.

Renal effects in the animal studies included vacuolation and focal necrosis of the kidney tubular epithelium, suppurative nephritis, mottled kidneys, renal papillary congestion and hemorrhage, pigment accumulation, tubulointerstitial nephritis, and kidney medulla mineralization. The safety factors for renal toxicity, based on the no-effect levels and the MRHD of 20 mg/day in a 60 kg patient on a mg/m² basis, were 39X, 15X, 16X, and 6.5X in mice, rats, dogs, and baboons, respectively, in the subchronic studies, and 10X, 29X, and 13X in rats, dogs, and baboons, respectively, in the chronic studies.

Other adverse effects of memantine HCl at high doses may include constipation, indicated by dose-related decreased intestinal motility in rats, and decreased blood pressure indicated by decreased systolic left ventricular blood pressure in dogs. Potential effects of memantine in the testes were suggested by lymphocytic infiltration, testicular atrophy, spermiogenesis disturbance with vacuolar degeneration in the germinal epithelium, and giant cells in the testes in the subchronic and chronic studies in rodents at doses representing 1X-10X the MRHD. Potential hematopoietic system effects were indicated by increased thromboplastin time at 3X-13X the MRHD, and increased erythroid cells without anemia at 6.5X-13X the MRHD in baboons treated for 13 weeks and 52 weeks, respectively.

Memantine showed no evidence of genotoxic potential in the Ames test, the Chromosome Aberration Assay in human lymphocytes, the metaphase analysis assay in rat spermatocytes, and in the Mouse Micronucleus test. However, because the results were equivocal in the Gene Mutation Assay in Chinese Hamster V79 cells, the mutagenic potential of memantine HCl cannot be ruled out. Memantine HCl was negative for carcinogenicity in standard 2-year assays

in mice and rats, at up to 10X the MRHD of 20 mg/day in a 60 kg patient on a BSA basis. Memantine HCl had no adverse effects on male and female fertility in rats, no teratogenic effects in rats and rabbits, and no adverse effects on perinatal and postnatal development in rats at doses up to 18 mg/kg/day (9X the MRHD on a BSA basis), although reduced growth and developmental delay were observed at 18 mg/kg/day in rats.

Three impurities were described with specifications greater than the threshold for qualification. These impurities,

, were appropriately qualified by inclusion at levels representing adequate multiples of the human exposure, in the drug batch used in the 2-year carcinogenicity studies in mice and rats and in the Mouse Micronucleus test.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

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Studies Reviewed in this NDA:

Examination of the influence of Memantine-HCl on several cardiovascular parameters and the respiration in anesthetised beagle dogs following intraduodenal administration. — Study 10053/96, Vol. 17, p. 75.

Subacute oral toxicity study on D145 in the dog (3 months). — Vol. 17, p. 129.

Six month chronic oral toxicity study of D145 in dogs. — 244006, Vol. 18, p. 1.

Subacute oral toxicity study on D145 over 12 months in the dog. — Vol. 21, p. 1.

Examination of the influence of Memantine-HCl on intestinal motility following oral administration (charcoal propulsion test in the rat). — Study 10054/96, Vol. 21, p. 235.

Examination of Memantine-HCl for spasmolytic or spasmogenic properties in the isolated guinea-pig ileum. — Study 10052/96, Vol. 21, p. 243.

Examination of the influence of Memantine-HCl on the diuresis and saluresis in rats following oral administration. — Study 10055/96, Vol 21, p. 259.

Examination of the effects of compounds on HERG channels. — Report #G0002M/001, Vol. 22, p. 30.

14-day dose-range-finding study of Memantine HCl in B6C3F1 mice by administration in the diet (to determine the palatability of the dietary treatment levels for a 13-week maximum tolerated dose-level (MTD) study). — Study 7195/92, Vol. 22, p. 114.

13-week dose-range-finding study of Memantine HCl in B6C3F1 mice by administration in the diet (to determine the maximum tolerated dose-level for a long-term feeding study in mice). — Study 7196/92, Vol 23, p. 1.

13-week dose-range-finding study of Memantine HCl in B6C3F1 mice by administration in the diet (to determine the maximum tolerated dose level for a long term feeding study in mice). Supplementary histopathology report. Addendum No. 1. — Study 7196/92, Vol. 25, p. 1.

Subacute oral toxicity study on Memantine in the rat. — Vol. 25, p. 241.

Memantine HCl – 6-week oral (dietary administration) comparative study in the pigmented and albino rat. — Study 442/011, Vol. 26, p. 1.

Memantine HCl – 6-week oral (dietary administration) comparative study in the pigmented and albino rat. Additional Histological Examination of the Brain. — Study 442/011, Vol. 26, p. 262.

Introduction and Drug History:

Memantine is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist with moderate affinity, with strong voltage-dependent characteristics and rapid channel unblocking kinetics. There is evidence that excessive neuronal calcium influx induced by overstimulation of the NMDA receptor during prolonged endogenous glutamate transmission is responsible for the pathophysiology and neuronal cell death associated with neurodegenerative central nervous system disorders, such as Alzheimer's disease. The rationale for the development of this drug product for the treatment of moderate to severe Alzheimer's dementia is based on the hypothesis that decreasing excessive glutamate transmission will attenuate excitotoxic neuronal destruction and improve cognitive function in patients with severe Alzheimer's disease. Memantine is approved and marketed in 41 countries, under the tradenames Akatinol®, Axura®, and Ebixa®. The currently marketed therapeutic dose and proposed dose in this submission is 20 mg/day. Fifty-three clinical trials were conducted in healthy volunteers and dementia patients, with 21 studies in 2625 patients ongoing at the time of the NDA submission. The clinical safety data indicate that memantine, at therapeutic doses of up to 20 mg/day, is well tolerated and produces minor dose-related adverse effects, including dizziness, headache, confusion, and constipation.

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Memantine HCl – 6 week-oral (dietary administration) comparative study in the pigmented and albino rat. Addendum 5 (Analytical results) and 6 (Histological procedure for eyes). Study 442/011, Vol. 27, p. 1.

A comparative optical toxicity study of SUN Y7017 by dietary administration in albino (SD) and pigmented (Long Evens) rats. Suntory Study ZR0001, Vol. 27, p. 53.

A repeated dose toxicity study of SUN Y7017 by dietary administration for 6 weeks and followed by a 4-week withdrawal period in Long Evans rats (a comparative toxicity study to SD rats). Suntory Study SR0004. N Vol. 27, p. 152.

Memantine HCl: 13-week oral (dietary administration) toxicity study in the rat, followed by a 4-week treatment free period. — Study 442/003, Vol. 28, p. 1.

A thirteen-week subacute toxicity study in rats fed diet-containing Memantine with a recovery of 5 weeks. — Study B-1717, Vol. 30, p. 1.

Report and expert statement on histological specimen from a 13-week subchronic toxicity study (B-1717) on rats fed a memantine containing diet. Vol. 30, p. 78.

Six month chronic oral toxicity study of NEU 3004 in the rat. — Study N002171A, Vol. 30, p. 94.

Chronic 12 month oral toxicity study with D145 in the rat. — , Vol. 31a, p. 202.

12 month oral toxicity study with D145 in rats. Compilation study results (using modern statistical methods). — Report 3-4-170-72, Vol. 32, p. 1.

Memantine HCl – 52-week oral (dietary administration) toxicity study in the rat followed by a 6-week treatment free period. — Study 442/007, Vol. 33, p. 1.

Memantine HCl – 52 week oral (dietary administration) toxicity study in the rat followed by a 6 week treatment free period. Additional histological examination of the brain. — Study 442/007, Vol. 36, p. 1.

Report and expert statement on histological specimen from a 52-week chronic toxicity study (442/007) in rats fed a memantine containing diet. Vol. 36, p. 28.

Memantine HCl – 52-week oral (dietary administration) toxicity study in the rat followed by a 6 week treatment free period. Electron microscopic examination of the retina. — Study 442/007, Vol. 36, p. 38.

Memantine: 13-week oral toxicity study in baboons with a 4-week withdrawal period. — Report PTX 46/861238, Vol. 36, p. 78.

Memantine: toxicity to baboons by repeated oral administration for 52 weeks followed by a 4-week withdrawal period. — Report PTX 48/8854. Vol. 37, 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. — Study Number 6277-146 (mouse), Vol. 37c, p. 492. Also in Amendment to the Pending NDA dated September 3, 2002, Vol. 1, Attachment 3.

Long-term feeding study of Memantine-HCl in B6C3F1 mice – carcinogenicity study. — Study 7279/92, Vol. 38, p. 1.

Pathology Working Group Report, Study 488-002.
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. Study 7280/92. Vol. 46, p. 1.

Long-term feeding study of Memantine-HCl in Sprague-Dawley rats – carcinogenicity study. Histopathology of the kidneys. — Study 7280a/92, Vol. 55, p. 1.

Memantine-HCl Carcinogenicity Study: Statistical report of rat survival and neoplastic lesions. — Study 6277-146, Amendment to the Pending NDA dated September 3, 2002, Vol. 1, p. 1.

Neurotoxic symptoms in female Sprague-Dawley rats following acute applications of the NMDA-antagonist memantine-HCl, D-30559
— Report dated 9 August 1995, Vol. 56, p. 15.

Memantine HCl: Olney lesions after acute and repeated oral dosing in male and female Sprague Dawley rats. Merz Report dated 4 June 1997, Vol 56, p. 66.

Neuronal vacuolization and necrosis after continuous infusion of the NMDA-receptor antagonist memantine HCl in the rat. — Study 9258/1/95, Vol. 56, p. 88.

Memantine-HCl: Toxicokinetic study in baboons (plasma and urine) by repeated oral administration for 14 days, Vol. 56, p. 160.

Determination of memantine in plasma of rats derived from study 9258/1/95. Study No. ZA045-95. + Risk assessment with regard to neuronal toxicity in human treatment with the NMDA-antagonist memantine-HCl. Summary of findings and discussion. Merz and Co., Report dated July 1997. Vol. 57, p. 148.

Memantine and metabolites: Memantine HCl toxicokinetic study in baboons (plasma and urine) by repeated oral administration for 14 days. Study No. PTX 52/932357. Merz Study No. ZA090-93/PTX52. Vol. 58, p. 1.

Investigation into the anterior eye segment lesion after chronic application of high dosages of Memantine HCl in two rat strains. Report 93-0-40/94-0-44. Vol. 58, p. 58.

Reproduction and fertility study with Memantine in the rat. — Study No. 064214. Vol. 59, p. 1.

Embryotoxicity (including teratogenicity) study with Memantine in the rat. Study No. 064225. Vol. 60, p. 1.

Effect of Memantine on pregnancy of the rabbit. — Study No. PTX 44/86149. Vol. 61, p. 1.

Peri- and postnatal study with Memantine in the rat. — Study No. 064236. Vol. 61, p. 86.

Ames metabolic activation test to assess the potential mutagenic effect of Memantine. Study No. PTX 8/80764. Vol. 61, p. 210.

Reverse mutation test of Memantine HCl in bacteria. — Study No. 89101M. Vol. 61, p. 221.

Gene mutation assay in Chinese hamster V79 cells *in vitro* with Memantine HCl. — Study No. 219510. Vol. 61, p. 235.

Chromosome aberration assays in human lymphocytes *in vitro* with Memantine HCl. — Study No. 219521. Vol. 61, p. 267.

Metaphase analysis on Memantine HCl. — Study No. PTX 21-82309. Vol. 61, p. 306.

Memantine HCl micronucleus test. — Report No. 5525-M-06496. Vol. 61, p. 327.

Mutagenicity study of MRZ 2/325 in the *Salmonella typhimurium* reverse mutation assay (*in vitro*). — Report No. 10551/97. Vol. 61, p. 356.

¹⁴C-Memantine hydrochloride placental transfer and metabolism studies in the rabbit following intravenous administration, Study PK-01-054. Submission dated April 11, 2003 (NDA 21-487 N (SLL)). Vol. 1, p. 173.

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Patch clamp studies on memantine and memantine metabolites demonstrated that memantine is a voltage-dependent, low affinity, uncompetitive (open channel) NMDA receptor antagonist. The metabolite MRZ 2/169 showed high potency, but the metabolites MRZ 2/371, MRZ 2/373, MRZ 2/374, and MRZ 2/375 were very weak antagonists at the NMDA receptor. MRZ 2/169 is excreted in the urine of dogs at approximately 5% total radioactivity, and is not detected in mice, rats, baboons, and humans. The memantine metabolite MRZ 2/325 (dimethyl-gludantan) was a very weak antagonist at four NMDA receptor subtypes in *Xenopus* oocytes, and is unlikely to be involved in memantine pharmacological effects in animals and humans.

In studies on drug activity related to the proposed indication, memantine increased locomotor activity in mice and rats, shortened the time to appearance of spontaneous movements in mice after head blow (return to consciousness, animal model of head injury), decreased the number of trials in a retention session in anoxia-treated mice, increased learning (avoidance rate) in rats with internal capsule lesions, increased hippocampal alpha power and maintained cortical beta2 power in freely moving rats, increased beta2 power and decreased alpha1 and alpha2 power in spontaneous cortical EEGs in cats, increased total power of rhythmic slow wave activity in the hippocampus after intraseptal administration in rats, antagonized the disturbed EEG patterns in pons ischemic rats, and increased DOPAC and HVA levels, but not the noradrenaline, MOPEG, dopamine, serotonin, and 5-HIAA levels in the nucleus accumbens in rats. Memantine had no effect on decreased locomotor activity in the retention session of a habituation assay, and the latency to enter the dark compartment at a retention session in cycloheximide-induced amnesia in mice.

Neuroprotective effects of memantine were observed in rats injected with beta-amyloid 1-40 (AB1-40) to induce hippocampal neuronal degeneration, a model of degeneration observed in Alzheimer's disease patients. Specifically, memantine administered subcutaneously by osmotic pump at 30 mg/ml for 9 days, producing steady state plasma concentrations of 1.40-3.58 mcM, decreased the extent of AB1-40 induced neuronal loss in the CA1 subfield, reduced the number of MAP2 positive somata indicating cytoskeletal alterations in several hippocampal areas, reduced the immunoreactivity for astroglial and microglial macrophage markers GFAP and ED1, and reduced apoptotic profiles in the hippocampus 7 days after AB1-40 injection.

II. SAFETY PHARMACOLOGY:

Neurological effects:

Memantine HCl, given by oral gavage at doses of 10, 30, and 100 mg/kg in mice, had no effect at the lowest dose on neuropharmacological parameters in the IRWIN test, including awareness (alertness, visual placing, passivity, and stereotypy), mood (grooming, vocalization, restlessness, and aggression), motor activity (reactivity, spontaneous activity, touch response, and pain response), CNS excitation (startle response, Straub tail, tremors, twitches, and convulsions), posture (body posture, limb position, staggering gait, abnormal gait, and righting reflex), muscle tone (limb tone, grip strength, body sag, body tone, and abdominal tone), reflexes (pinna,

corneal, and ipsilateral flexor reflex), and autonomic function (writhing, pupil size, palpebral opening, exophthalmus, urination, salivation, piloerection, hypothermia, skin color, and respiration rate). At 30 mg/kg PO, there was 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). The 100 mg/kg dose affected most of the parameters measured, including decreased awareness, motor activity, CNS excitation, muscle tone, reflexes, and autonomic function (respiratory rate). In another study, memantine increased spontaneous motility in mice at oral doses of 5-80 mg/kg in a dose-related manner, but the effects were 15X-20X less than those by d-amphetamine at 1-2.5 mg/kg. There was a dose-related increase in sleeping time in male and female mice administered memantine at oral doses of 15, 30 (50% increase) and 60 mg/kg (100%).

Potential anticonvulsive properties of memantine HCl were investigated in mice administered doses of 10-33 mg/kg orally. Electroshock-induced (165V, 45mA, 0.7 sec stimulus duration) convulsions, induced 60 minutes after dosing, were decreased significantly in a dose-related manner by 0, 40%, 60%, and 100% at 10, 15, 22, and 33 mg/kg memantine, respectively. The ED₅₀ (dose that prevented convulsions in 50% mice) was 18.4 mg/kg oral memantine HCl. In comparison, diazepam at 20 mg/kg PO provided 80% protection from the tonic convulsions induced by electroshock in the mice.

Oral memantine HCl increased the number of pentetrazol-induced (110 mg/kg SC given 60 minutes after memantine dosing) convulsions by 167% at 22 mg/kg and 256% at 33 mg/kg PO in mice. The control article, diazepam (25 mg/kg) completely blocked the convulsions induced by pentetrazol. In another study, memantine HCl induced convulsions in 10%, 80%, and 100% mice at the doses of 10, 30, and 100 mg/kg PO (ED₅₀ 17.8 mg/kg PO) when given 60 minutes prior to subthreshold doses of pentetrazol (50 mg/kg SC). The positive control article, d-amphetamine (50 mg/kg) induced convulsions in 40% mice given the subconvulsive dose of pentetrazole. Memantine HCl had no pro-convulsive effects when given at doses of 10-100 mg/kg PO 60 minutes prior to subthreshold (24V, 5 mA, 0.8 sec stimulus duration) electrical current in mice, while the positive control article, bemegride at 20 and 40 mg/kg PO, induced convulsions in 40% and 100% mice, respectively.

In a safety pharmacology study on potential effects of memantine HCl on body temperature in mice, reserpine was administered at 5 mg/kg IP, 60 minutes after dosing with memantine at 10, 30, and 100 mg/kg PO. Reserpine given alone reduced body temperature by 10 °C. Memantine antagonized the reduction in body temperature (-7 °C at all doses tested at 4 hours after reserpine treatment) without a relationship to dose in the magnitude of effect.

Cardiovascular effects:

Study title: Examinations of the effects of compounds on HERG potassium channels

Key study findings:

- Memantine and MRZ 2/579 reduced HERG inward tail current amplitude approximately 13% at 100 mcM, amantadine by 27% at 500 mcM, MRZ 2/705 by 52% at 100 mcM, budipine by 100% at 100 mcM

- Memantine had minor effects on HERG potassium channel function, indicated by approximately 29% reduction in the fluorescence assay and 13% when measured by electrophysiology

Study no: — No. G0002M/001

Volume # 22, and page # 30

Conducting laboratory and location: —

Date of study initiation: Report date February 10, 2000

GLP compliance: yes () no (x)

QA report: yes () no (x)

Drug RNMZRZ 1 (Memantine), lot # Not provided, radiolabel Not applicable, and % purity Not provided

Formulation/vehicle: See under Methods, below

Methods (unique aspects): Stably transfected Chinese hamster ovary cells were tested using the fluorescence assay and electrophysiology recordings to evaluate memantine (10, 30, and 100 mcM), MRZ 2/579 (10, 30, and 100 mcM), budipine (10, 30, and 100 mcM), MRZ 2/705 (10, 30, and 100 mcM), and amantadine (50, 150, and 500 mcM) effects on HERG potassium channel (Human ether-a-gogo gene) function. The test substances were dissolved in water (100 mM), except for MRZ 2/705 which was dissolved in 50% DMSO at 25 mM. In the fluorescence assay, the HERG cells and wild-type CHO cells (controls) were dye-loaded — incubated with the test articles, and relative changes of fluorescence were measured (change in control cells - HERG cells). The fluorescence assay was performed in triplicate. In the electrophysiology assay, the CHO cells (n=3-9) were whole-cell patch clamped at -60 mV, depolarized from holding potential to +40 mV for 1 second, and hyperpolarized or depolarized in 20 mV increments for 300 msec to -120 to +20 mV, at 0.1 Hz. The cells were depolarized from holding potential to +40 mV for 300 msec, and repolarized at 0.5 mV/msec to -60 mV, followed by test potential to -120 mV for 200 msec. The test articles were added and the cells were stimulated 44 times, with analysis of peak inward tail-currents. Current/voltage relationship was analyzed at steady state.

Results: Fluorescence assay: The results of fluorescence assay are presented in the following table (reproduced from the original NDA submission):

Results of the Fluorescence Assay: Relative Remaining Activity

Compound	100 mcM	30 mcM	100 mcM
Memantine	0.88	0.81	0.71
MRZ 2/579	0.92	0.86	0.69
Budipine	0.61	0.36	0.00
MRZ 2/705	0.87	0.89	0.83
Compound	50 mcM	150 mcM	500 mcM
Amantadine	0.96	0.91	0.73

Electrophysiology assay: The results of the electrophysiology assay are presented in the following table (reproduced from the original NDA submission):

Electrophysiology Assay: Relative Remaining Current Amplitudes (mean \pm S.D.)

Compound	100 mcM	30 mcM	100 mcM
Memantine	1.00 \pm 0.01	0.97 \pm 0.03	0.85 \pm 0.05
MRZ 2/579	0.98 \pm 0.03	0.96 \pm 0.04	0.88 \pm 0.05
Budipine	0.31 \pm 0.05	0.16 \pm 0.07	0.04 \pm 0.03
MRZ 2/705	0.93 \pm 0.10	0.77 \pm 0.08	0.48 \pm 0.05
Compound	50 mcM	150 mcM	500 mcM
Amantadine	0.90 \pm 0.09	0.80 \pm 0.05	0.73 \pm 0.06

Study title: Examination of the influence of memantine HCl on several cardiovascular parameters and the respiration in anesthetized beagle dogs following intraduodenal administration

Key study findings:

- Dose-related decrease in cardiac minute output at 10 mg/kg (7.5%) and 30 mg/kg (20%), and stroke volume at 10 mg/kg (14%) and 30 mg/kg (32%), compared to controls, 10 minutes after dosing
- Systolic left ventricular blood pressure decreased at 30 mg/kg compared to control, at 15 (9%) and 30 (18%) minutes after dosing

Study no: — 10053/96

Volume # 17, and page # 75

Conducting laboratory and location: _____

Date of study initiation: January 28, 1997

GLP compliance: yes () no (x)

QA report: yes () no (x)

Drug Memantine HCl, lot # Not provided, **radiolabel** Not applicable, and **% purity** Not provided

Formulation/vehicle: Test article dissolved in

Methods (unique aspects):

Dosing:

Species/strain: Purebred Beagle dogs

#/sex/group or time point (main study): 5 females (each received all doses at ascending levels, 60 minutes apart)

Satellite groups used for toxicokinetics or recovery: None

Age: Not provided

Weight: 11.7-12.8 kg

Doses in administered units: 3, 10 and 30 mg/kg

Route, form, volume, and infusion rate: Oral by intraduodenal gavage at 10 ml/kg

Observations and times: The dogs were intubated and ventilated (15 cycles/minute respiratory rate, 10% oxygen) under chloralose-urethane anesthesia, and received continuous Ringer solution (5 ml/kg/h) to maintain body fluid and external heating to maintain body temperature at

38 °C. Memantine HCl was administered by intraduodenal gavage using a fixed catheter at ascending doses, 60 minutes apart. The measurements were peripheral arterial blood pressure (systolic and diastolic) using an intraarterial probe catheter in the right arteria femoralis, systolic, diastolic and capillary pressure (pulmonary, wedge pressure) using a floating balloon catheter in the a. pulmonalis, heart rate using a _____ cardiac minute output and cardiac stroke volume using the cold dilution method, left ventricular pressure (dp/dt max) using an X-ray positive catheter in the left ventricle, central vein pressure using a probe catheter and _____ in the anterior vena cava caudalis, and arterial oxygen supply using blood gas analysis (arterial pH, oxygen saturation, partial carbon dioxide pressure, partial oxygen pressure, and hydrogen carbonate). The measurements were conducted at baseline and for 30 minutes after each drug administration. L-noradrenaline HCl (2 mcg/kg IV) and isoproterenol hemisulfate (2 mcg/kg IV) were administered before the first observation period and at the end of the last observation period.

Results: There were no treatment-related effects of oral memantine HCl at doses of 3, 10 and 30 mg/kg on circulatory function parameters (peripheral systolic and diastolic arterial blood pressure, heart rate, cardiac minute output, stroke volume, mean left systolic ventricular pressure, dp/dt max, pulmonary systolic and diastolic arterial blood pressure, wedge pressure, and central vein pressure), respiratory function parameters (blood pH, pO₂, pCO₂, blood oxygen saturation, and blood HCO₃ concentration), when compared to baseline (pre-dose) values. There were no treatment-related effects of memantine HCl on the reaction to noradrenaline and isoproterenol.

When compared to the responses following vehicle administration, there was a decrease in cardiac minute output at 10 mg/kg (7.5%), and a significant decrease in cardiac minute output at 30 mg/kg (20%) and stroke volume at 10 (14%) and 30 (32%) mg/kg, 10 minutes after dosing. Systolic left ventricular blood pressure was decreased at 30 mg/kg when compared to vehicle control, at 15 (9%) and 30 (18%) minutes after dosing.

Renal effects:

Study title: Examination of the influence of memantine-HCl on the diuresis and saluresis in rats following oral administration

Key study findings:

- Increased urine volume 2-5 hours after dosing at 40 mg/kg PO, highest at 2 hours (48% higher than control); positive control article furosemide induced 30% increase over control), no differences from control observed for the 24-hour period after dosing
- Dose-related increase in sodium and chloride excretion at all doses from 10-40 mg/kg PO from 2-5 hours after dosing (greatest increases in second hour after dosing), no differences from control values overall for 24-hour period after dosing
- Sodium excretion increased 126%, 188%-241%, and 205%-276% at 10, 20 and 40 mg/kg memantine, respectively, compared to 232%-403% by furosemide during 5-hour period after dosing
- Chloride excretion increased 124%-184% and 120%-197% at 20 and 40 mg/kg, respectively, compared to 293%-637% by furosemide during 5-hour period after dosing
- NOAEL for increased diuresis and saluresis not identified (<10 mg/kg PO)

- Doses studied were 5X-19X the MRHD of 20 mg in a 60 kg patient on a BSA basis

Study no: — 10055/96

Volume # 21, and page # 259

Conducting laboratory and location: _____

Date of study initiation: January 9, 1997

GLP compliance: yes (x) no ()

QA report: yes () no (x)

Drug Memantine HCl, lot # R 7206, radiolabel Not applicable, and % purity 99.3%-99.7%

Formulation/vehicle: Test article dissolved in water for injection

Methods (unique aspects):

Dosing:

Species/strain: Sprague-Dawley/Crl: CD®BR rats (_____)

#/sex/group or time point (main study): 10 females/dose

Satellite groups used for toxicokinetics or recovery: None

Age: Not provided

Weight: 158-186 g

Doses in administered units: 0, 10, 20, and 40 mg/kg

Route, form, volume, and infusion rate: Oral by gavage at 50 ml/kg

Observations and times: The positive control article was furosemide (20 mg/kg) dissolved in 0.8% aqueous hydroxypropyl-methylcellulose gel, given orally by gavage. The rats were administered memantine HCl, negative control (vehicle) or positive control, and urine was collected for the following periods after dosing: 0-1, 1-2, 2-3, 3-4, 4-5, and 5-24 hours. The measures were urine volume, and urine sodium, potassium, and chloride concentrations.

Results: The results of the urine volume, sodium, potassium and chloride measurements are presented in the following table:

Cumulative Urine Volume, and Sodium, Potassium and Chloride Excretion over 24 hours after Dosing in Rats Administered Oral Memantine HCl (Percent Change from Control Value in Parentheses)

Dose (mg/kg)	Collection Period (Hours after Dosing)					
	0-1	0-2	0-3	0-4	0-5	0-24
Urine Volume (ml/kg bw, mean ± S.D.)						
Vehicle	16.3 ± 10.8	34.9 ± 11.8	44.1 ± 10.4	46.6 ± 5.19	47.4 ± 5.17	67.4 ± 6.27
Memantine 10	20.6 ± 5.86	43.2 ± 6.71	47.5 ± 7.06	48.5 ± 7.4	48.5 ± 7.36	64.0 ± 8.06
Memantine 20	17.4 ± 12.2	43.0 ± 15.6	48.7 ± 11.4	51.3 ± 8.05	52.3 ± 8.08	65.1 ± 10.6
Memantine 40	17.4 ± 9.29	51.7 ± 13.18** (+48%)	57.8 ± 5.59** (+31%)	58.1 ± 8.69** (+25%)	58.5 ± 8.78** (+23%)	69.6 ± 8.79
Furosemide 20	26.3 ± 9.23	45.4 ± 6.45	47.6 ± 7.19	48.0 ± 7.89	48.9 ± 7.88	66.2 ± 7.58
Sodium (mmol/kg bw, mean ± S.D.)						
Vehicle	0.26 ± 0.14	0.28 ± 0.18	0.34 ± 0.18	0.39 ± 0.20	0.43 ± 0.27	2.38 ± 0.61
Memantine 10	0.23 ± 0.15	0.58 ± 0.31	0.77 ± 0.39** (+126%)	0.79 ± 0.41	0.79 ± 0.41	2.55 ± 0.74
Memantine 20	0.18 ± 0.16	0.88 ± 0.55** (+214%)	1.16 ± 0.59*** (+241%)	1.22 ± 0.63*** (+213%)	1.24 ± 0.65*** (+188%)	2.64 ± 0.86

Memantine 40	0.30 ± 0.22	1.04 ± 0.53*** (+271%)	1.28 ± 0.47*** (+276%)	1.31 ± 0.48*** (+236%)	1.31 ± 0.48*** (+205%)	2.87 ± 0.63
Furosemide 20	1.19 ± 0.60*** (+357%)	1.41 ± 0.60*** (+403%)	1.42 ± 0.60*** (+318%)	1.42 ± 0.61*** (+264%)	1.43 ± 0.60*** (+232%)	2.54 ± 0.534
Potassium (mmol/kg bw, mean ± S.D.)						
Vehicle	0.20 ± 0.12	0.28 ± 0.17	0.44 ± 0.19	0.48 ± 0.20	0.53 ± 0.26	3.33 ± 0.52
Memantine 10	0.20 ± 0.11	0.37 ± 0.17	0.57 ± 0.22	0.64 ± 0.27	0.64 ± 0.27	3.22 ± 0.77
Memantine 20	0.12 ± 0.06	0.40 ± 0.19	0.64 ± 0.34	0.77 ± 0.50	0.86 ± 0.65	3.02 ± 1.12
Memantine 40	0.18 ± 0.13	0.42 ± 0.21	0.58 ± 0.29	0.61 ± 0.29	0.65 ± 0.39	3.39 ± 1.11
Furosemide 20	0.56 ± 0.17	0.77 ± 0.20*** (+175%)	0.80 ± 0.20*** (+82%)	0.82 ± 0.21** (+71%)	0.86 ± 0.19** (+62%)	3.26 ± 0.50
Chloride (mmol/kg bw, mean ± S.D.)						
Vehicle	0.24 ± 0.18	0.31 ± 0.20	0.48 ± 0.21	0.55 ± 0.17	0.59 ± 0.27	2.20 ± 0.62
Memantine 10	0.22 ± 0.16	0.55 ± 0.32	0.76 ± 0.44	0.81 ± 0.51	0.81 ± 0.51	2.25 ± 0.66
Memantine 20	0.12 ± 0.09	0.88 ± 0.50** 0.89 (+184%)	1.22 ± 0.60** (+154%)	1.30 ± 0.68** (+136%)	1.32 ± 0.71** (+124%)	2.33 ± 0.56
Memantine 40	0.22 ± 0.14	0.92 ± 0.40*** (+197%)	1.23 ± 0.36*** (+156%)	1.26 ± 0.37*** (+129%)	1.30 ± 0.38*** (+120%)	2.64 ± 0.71
Furosemide 20	1.77 ± 0.71*** (+637%)	2.24 ± 0.69*** (+622%)	2.29 ± 0.70*** (+377%)	2.30 ± 0.71*** (+318%)	2.32 ± 0.70*** (+293%)	2.89 ± 0.59

p<0.01 compared to vehicle; *p<0.001 compared to vehicle

Gastrointestinal effects:

Study title: Examination of the influence of memantine-HCl on intestinal motility following oral administration (charcoal propulsion test in the rat)

Key study findings:

- Dose-related inhibition of intestinal motility by memantine HCl (0%, 40%, 50%, and 60% animals with no charcoal in the cecum at 0, 10, 20, and 40 mg/kg PO, ED50 20 mg/kg PO) measured 4 hours after dosing by gastric intubation

Study no: — 10054/96

Volume # 21, and page # 237

Conducting laboratory and location: —

Date of study initiation: November 22, 1996

GLP compliance: yes () no (x)

QA report: yes () no (x)

Drug Memantine HCl, lot # Not provided, radiolabel Not applicable, and % purity Not provided

Formulation/vehicle: Test article dissolved in water for injection

Methods (unique aspects):

Dosing:

Species/strain: Female Sprague-Dawley rats

#/sex/group or time point (main study): 10/dose

Satellite groups used for toxicokinetics or recovery: None

Age: Not provided

Weight: Not provided

Doses in administered units: 0, 10, 20, and 40 mg/kg

Route, form, volume, and infusion rate: Oral, by gastric intubation at 10 ml/kg

Observations and times: One hour after drug or vehicle administration, the rats received 10% charcoal and 5% gum acacia (gum arabic) at 10 ml/kg in aqueous suspension by gastric intubation. The rats were sacrificed 3 hours after the charcoal treatment, and intestines isolated from the stomach cardia to the anus. The intestines were inspected for distance traveled by the charcoal, and inhibition of intestinal motility was deemed positive if no charcoal was found in the cecum and negative for inhibition of intestinal motility if the contents of the cecum were black.

Results: There was a dose-related inhibition of intestinal motility by memantine HCl (0%, 40%, 50%, and 60% rats with no charcoal in the cecum at 0, 10, 20, and 40 mg/kg PO, ED50 20 mg/kg PO).

Study title: Examination of memantine-HCl for spasmolytic or spasmogenic properties in the isolated guinea-pig ileum

Key study findings:

- Spasmogenic effect at 1×10^{-5} g/ml (slight), a greater effect at 1×10^{-4} g/ml (26% effect caused by acetylcholine) and 1×10^{-3} g/ml (9% effect caused by acetylcholine)
- Agonist effect not antagonized by papaverine (3×10^{-5} g/ml), antazoline (3×10^{-8} g/ml), and atropine (3×10^{-8} g/ml)
- Concentration-related spasmolytic (antagonist) effects at 1×10^{-5} g/ml, with complete antagonism of agonist-induced (acetylcholine (5×10^{-7} g/ml), histamine (5×10^{-8} g/ml), barium chloride (2×10^{-4} g/ml), and 5-hydroxy-tryptamine (1.5×10^{-8} g/ml) contractions at 1×10^{-4} g/ml.

Study no: — 10052/96

Volume # 21, and page # 243

Conducting laboratory and location: —

Date of study initiation: November 12, 1996

GLP compliance: yes () no (x)

QA report: yes () no (x)

Drug Memantine HCl, lot # Not provided, radiolabel Not applicable, and % purity Not provided

Formulation/vehicle: Test article dissolved in water for injection

Methods (unique aspects):

Dosing:

Species/strain: — Hartley guinea-pigs

#/sex/group or time point (main study): 6 females/test article concentration

Satellite groups used for toxicokinetics or recovery: None

Age: Not provided

Weight: 388-510 g

Doses in administered units: 1×10^{-9} , 1×10^{-8} , 1×10^{-7} , 1×10^{-6} , 1×10^{-5} , 1×10^{-4} , 1×10^{-3} g/ml

Route, form, volume, and infusion rate: Test article dissolved in water for injection was added to organ bath at 25 ml, exposure 2 minutes, tissues were exposed to all test article concentrations in sequentially increasing doses, separated by 5 minute washout between doses using Tyrode's solution

Observations and times: The guinea-pigs were sacrificed and ileum isolated, removed (25-30 cm length), and washed with Tyrode's solution. A 1 ½ cm section of ileum was suspended in aerated Tyrode's solution bath, with ends attached to the bath base and a lever, with which ileum movements were recorded using a Multi-Pen Recorder (initial load 1.0 g). Test article was added to the tissue bath and amplitude of tissue movement (contraction force) was recorded in mm. Percent change was calculated and compared to positive control article induced changes (acetylcholine, 5×10^{-7} g/ml). Agonist effects were tested using 2-minute exposures to the following antagonists: papaverine (3×10^{-5} g/ml), antazoline (3×10^{-8} g/ml), and atropine (3×10^{-8} g/ml). A spasmolytic (antagonist) effect of memantine HCl was tested by application after 2-minute exposure to the agonists acetylcholine (5×10^{-7} g/ml), histamine (5×10^{-8} g/ml), barium chloride (2×10^{-4} g/ml), and 5-hydroxy-tryptamine (1.5×10^{-8} g/ml).

Results: The results of the contraction force measurements in isolated guinea pig ileum are presented in the following table:

Agonist and Antagonist Effects of Memantine HCl in Isolated Guinea Pig Ileum

Parameter*	Memantine HCl Concentration (g/ml)						
	1×10^{-9}	1×10^{-8}	1×10^{-7}	1×10^{-6}	1×10^{-5}	1×10^{-4}	1×10^{-3}
Agonist Effect (%Maximum Response)	0.0	0.00	0.00	0.00	6.38	25.57	8.75
Antagonist Effect (Reduction in %Maximum Response to Acetylcholine, Complete effect = 100%Atropine Effect)	2.08	4.30	1.78	2.17	21.35	82.75	100.00
Antagonist Effect (Reduction in %Maximum Response to Histamine, Complete Effect=100 %Antazoline Effect)	0.78	0.00	0.00	1.75	24.58	99.63	100.0
Antagonist Effect (Reduction in %Maximum Response to Barium Chloride Complete Effect=100%Papaverine Effect)	1.60	0.77	0.00	0.77	35.33	100.0	100.0
Antagonist Effect (Reduction in %Maximum Response to 5-HT, Complete Effect=100% Memantine effect)	3.03	9.47	6.43	5.47	1.32	84.73	100.0

*Maximum Agonist Response = 100% effect of acetylcholine at 5×10^{-7} g/ml; Antagonists for comparison were atropine at 3×10^{-8} g/ml, antazoline at 3×10^{-8} g/ml, barium chloride at 2×10^{-4} g/ml, and 5-hydroxy-tryptamine (5-HT) at 1.5×10^{-8} g/ml; Agonists for comparison were papaverine at 3×10^{-5} g/ml, antazoline at 3×10^{-5} g/ml, and atropine at 3×10^{-8} g/ml.

Abuse liability: In an intravenous self-administration assay, morphine-dependent, but not morphine-naïve mice self-administered memantine and MRZ 2/579, and memantine and MRZ 2/579 attenuated the severity of morphine withdrawal in the dependent mice. Intraperitoneal memantine injections produced significant conditioned place preference at the dose of 30 mg/kg, but not at lower doses, in Adult male Wistar rats. However, in another test, repeated IP

memantine injections at up to 30 mg/kg did not induce conditioned motor activity after repeated memantine-environment pairings. Although memantine partially substituted for PCP in drug discrimination studies in rats and monkeys, the rates of responding were significantly decreased, except at high doses.

III. PHARMACOKINETICS/TOXICOKINETICS:

PK parameters:

Intraperitoneal memantine HCl pharmacokinetics were studied in female Sprague Dawley rats administered single doses of 12.5, 25, and 50 mg/kg. The results are presented in the following table:

Pharmacokinetic Parameters in Female Rats Administered Single Dose Intraperitoneal Memantine HCl

Parameter	12.5 mg/kg	25 mg/kg	50 mg/kg
C _{max} (ng/ml)	779	3240	6590
T _{max} (h)	1.0	0.5	0.5
AUC _{0-6h} (ng.h/ml)	3130	8070	18200
AUC _{0-24h} (ng.h/ml)	4490	12300	30400
AUC _{0-inf} (ng.h/ml)	4510	12600	30900
T _{1/2} (h)	3.15	4.45	4.46
Cl _{tot} (ml/min)	38.4	27.5	22.4
V _z (L)	10.5	10.6	8.67

The increases in peak plasma levels and exposure (AUC values) were greater than linear. The AUC increased approximately 2.5X when the memantine dose was doubled. Peak plasma levels were observed at approximately 0.5-1 hour after dosing (T_{max}), and the half-life was 3-4.5 hours. Clearance was rapid (22.4-38.4 ml/min) and the large volume of distribution (8.7-10.6 L) suggested extensive tissue distribution.

The results of pharmacokinetic evaluation in male and female Sprague Dawley rats administered single oral doses of memantine are presented in the following table:

Pharmacokinetic Parameters in Rats Administered Single Oral Doses of Memantine HCl

	25 mg/kg 20.75 mg/kg free base		50 mg/kg 41.50 mg/kg free base		100 mg/kg 83.00 mg/kg free base	
	Males	Females	Males	Females	Males	Females
C _{max} (ng/ml)	1040	1640	2390	2440	4360	4940
T _{max} (h)	0.5	0.5	0.5	0.5	0.5	1.0
AUC _{0-inf} (ng.h/ml)	6403	9813	18424	25492	52158	79681
T _{1/2} elim (h)	5.74	5.69	7.04	9.36	6.70	9.39
Cl _{tot} (ml/min)	54.0	35.2	37.5	27.1	26.5	17.4
V _z (l)	26.8	17.4	22.9	22.0	15.4	14.1

There was a linear increase in peak plasma concentration (C_{max}) with dose and 2.5X-3.1X increase in exposure (AUC) values as the dose was doubled. The C_{max} was higher and AUC considerably higher in the female rats than in the male rats. The peak plasma concentrations were observed at 0.5 hours across doses, and half-life of elimination increased slightly with dose

from 5.7 h to 7-9.4 hours at 25 and 50-100 mg/kg memantine. Clearance decreased with dose. The high volume of distribution values (14-27 L) indicated extensive tissue distribution.

Male and female baboons were administered 8 mg/kg/day memantine HCl (dietary) daily for 14 days. The results of the pharmacokinetic evaluation are presented in the following table:

Pharmacokinetic Parameters (Means \pm S.D.) in Baboons Administered Dietary Memantine HCl at 8 mg/kg/day for 14 Days

Parameter	Day 1	Day 12
AUC _{0-t} (ng.h/ml)	1860.0 \pm 304.0	3630.0 \pm 789.0
AUC _{0-inf} (ng.h/ml)	2020.0 \pm 257.0	3890.0 \pm 961.0
C _{max} (ng/ml)	218.0 \pm 82.3	397.0 \pm 99.6
T _{max} (h)	2.25 \pm 1.26	2.50 \pm 1.73
T _{1/2} (h)	6.44 \pm 1.30	5.73 \pm 1.03
V _d (L)	37.7 \pm 11.5	17.2 \pm 1.3
Cl _{tot} (ml/min)	66.80 \pm 8.56	35.7 \pm 7.5
MRT (h)	9.93 \pm 2.23	8.82 \pm 1.06

In baboons administered memantine at the dose of 8 mg/kg/day in the diet for 12 consecutive days, the peak plasma levels (C_{max}) and exposure (AUC) increased 100% on Day 12 (397 ng/ml and 3600-3900 ng.h/ml, respectively) compared to the levels observed on Day 1 (218 ng/ml and 1860-2020 ng.h/ml, respectively). There was no change in T_{max} (approximately 2.25-2.50 h), and the half-life was slightly decreased with repeated dosing from 6.44 hours on Day 1 to 5.73 hours on Day 12. The volume of distribution (38 L on Day 1 and 17 L on Day 12) indicated extensive tissue distribution. Clearance was rapid, at 67 and 36 ml/min on Days 1 and 12, respectively.

A comparative pharmacokinetics study showed considerably lower elimination half-lives in dogs and baboons (between 4.4 and 10.2 hours) than in humans (52-58 hours) after oral administration of memantine. Also, the concentration of ¹⁴C-memantine in blood was higher than that in plasma in the humans, whereas in baboons and dogs, the concentrations were higher in plasma.

Absorption: Absorption of memantine HCl in male Sprague Dawley rats administered single doses of 0.5-12 mg/kg by oral gavage was rapid, producing peak plasma levels within 0.5-2 hours of dosing. In that study, based on the ratio of urinary to fecal radioactivity excretion of 4:1, respectively, it was estimated that approximately 80% oral memantine was absorbed, regardless of dose.

Distribution: In male Sprague Dawley rats administered a single dose of ¹⁴C-memantine HCl at 12 mg/kg by oral gavage, the highest concentrations (0.4-0.9 mg/kg) were found in the testicles, lungs, liver, kidneys, and intestinal fat at 24 hours after dosing. Lower concentrations (0.3-0.8 mg/kg) were found in brain, muscle and blood. The relative tissue and organ distribution was similar at the dose of 0.5 mg/kg PO; therefore, a linear dose-dependence of distribution processes is assumed. After repeated dosing at 12 mg/kg/day for 5 consecutive days, the concentrations in the tissues were increased by 2.6X over those after administration of single doses. At the dose of 0.5 mg/kg/day, tissue radioactivity was 2.1X higher after repeated dosing for 10 consecutive days than observed after a single administration. No increase in tissue concentrations were observed after 10 days of consecutive dosing when compared to the levels measured after 5

dosing days. The highest concentrations after repeated dosing were found in the testicles, lungs, liver and kidneys.

Male Wistar rats received a single oral gavage dose of ^{14}C -memantine HCl at 25 or 125 mg/kg, or a single intravenous dose of 5 mg/kg. Radioactivity measurements at 2, 4, 6, and 24 hours after dosing at 25 mg/kg PO showed peak plasma levels at 2 hours (1.6 mcg eq./ml), that decreased to 0.1 mcg eq./ml at 24 hours. At 125 mg/kg PO, peak plasma levels were observed at 6 hours (8.58 mcg eq./ml), and plasma radioactivity declined to 1.50 mcg eq./ml at 24 hours after dosing. Autoradiography measurements at 5 minutes (IV administered rats), or at 0.5, 2, 4, 8, 24, and 72 hours (25 mg/kg PO) after dosing showed highest radioactivity levels in the lung, liver, kidneys, brain, muscle, and lacrimal gland, in order of decreasing concentration, at 2 and 4 hours after dosing with 25 mg/kg PO. Tissue radioactivity levels at the 125 mg/kg PO dose, in order of decreasing concentration, were highest in the liver, lungs, kidneys, lacrimal glands, brain, eyelids, eyeballs, muscle, and red blood cells at 2 and 6 hours after dosing. At 24 hours after dosing, trace concentrations of radioactivity were detected in lung, liver, kidney, lacrimal gland and testicles, and at 72 hours radioactivity was found in the lung but no other tissues. After IV dosing (5 mg/kg), the highest concentrations of radioactivity were found in the lungs, kidneys, submaxillary gland, muscle, heart, lacrimal gland, pancreas, and gastrointestinal tissues, in decreasing order of concentration. The concentrations of radioactivity in the tissues at 5 minutes after dosing were higher than in the plasma. Radioactivity in the eyeball was predominantly in the cornea, sclera/choroid/retina, with lower concentrations in the lens and vitreous body.

Quantitative autoradiography in male albino and pigmented rats given a single oral gavage dose of ^{14}C -memantine at 80 mg/kg revealed rapid absorption and distribution to body tissues, with maximum concentrations at 1-6 hours after dosing in both strains, except for peak uveal tract and pigmented skin concentrations at 6-12 hours in the pigmented rats. The highest concentrations were found in the gastrointestinal tract, kidneys, urinary tract, liver, adrenal, lachrymal glands, Harderian gland, salivary glands and spleen in both strains, and in the eye and particularly in the uvea (vascular layer of the eyeball) in the pigmented rats. Higher concentrations of radioactivity were found in the eyes of the pigmented rats than in the albino eyes. Peak eye concentrations, observed at 6 hours after dosing, were 83.51 mcg eq/g in the pigmented rats and 8.81 mcg eq/g in the albino rats. At 96 hours after dosing, the eye radioactivity concentrations were 5.6 mcg eq/g in the pigmented and 0.13 mcg eq/g in the albino rats. Trace levels of radioactivity (0.277 mcg eq/g) were found in the pigmented rats' eyes at 28 days after drug administration. Most of the radioactivity in the eyes was concentrated in the uvea.

The quantitative tissue distribution measurements (mcg equivalents memantine base/g tissue) in pregnant New Zealand White rabbits administered 10 mg/47 mCi/kg memantine by single intravenous injection are presented in the following table*:

Tissue/Organ	30 minutes	1 hour	4 hours	24 hours	72 hours
Plasma	5.3	5.6	2.5	0.12	0.03
Whole blood	4.5	4.5	2.1	0.12	0.01
Brain	24.3	23.3	10.9	0.13	0.06
Eyes	2.4	2.5	1.0	0.08	0.03
Heart	13.5	11.5	5.1	0.51	0.47
Kidneys	74.3	75.2	46.1	2.14	0.79
Liver	12.9	19.7	7.7	1.15	0.85

Lungs	100.4	115.6	54.2	1.27	0.80
Amniotic fluid	0.6	0.6	0.5	0.24	0.06
Mammary glands	10.6	8.8	3.6	0.21	0.09
Ovaries	29.2	24.1	11.4	0.30	0.11
Placenta	12.8	8.5	5.2	0.26	0.06
Uterus	9.6	10.2	5.3	0.20	0.04
Fetal blood	2.0	1.9	1.2	0.18	0.03
Fetal Liver	12.3	10.9	4.5	0.17	0.06
Fetal carcass	5.1	4.3	1.7	0.15	ND

***Study PK-01-054 entitled ¹⁴C-Memantine Hydrochloride Placental Transfer and Metabolism Studies in the Rabbit Following Intravenous Administration (Submission N(SLL) dated April 11, 2003, Vol. 1, p. 173)**

The results showed that maximal plasma radioactivity concentrations occurred at 1 hour after dosing, and declined in a biphasic manner. The tissue concentrations were highest at 30 minutes after dosing, and highest in lungs, kidneys, ovaries, brain and liver. Memantine crossed the blood brain barrier and placenta. Fetal memantine concentrations were highest at 30 minutes after dosing, and similar to maternal levels in fetal blood and liver at that timepoint.

In baboons administered 5 mg/kg ¹⁴C-memantine HCl twice daily for 7 days, the highest tissue concentrations were observed, in decreasing order of concentration, in the bile, colon contents, kidneys, liver, lungs, medulla oblongata, spleen, lymph nodes, gonads, spinal cord, stomach contents, gyrum prae- and postcentralis, thalamus, and cingulum at 24 hours after the last dose. By 96 hours after the last dose, the highest concentrations were found in the bile, lungs, kidneys, adrenals, skin, spleen, liver, and colon contents.

An *in vitro* study was conducted to evaluate the potential for memantine to bind with melanin. ¹⁴C-memantine was dissolved at concentrations of 0.06, 0.60, 2.50, 6.00, 60, and 180 mcmol/7ml in a pigment suspension containing synthetic melanin, allowed to stand for 15 minutes, and then centrifuged. The radioactivity of the supernatant was measured by scintillation counting or the α assay, and the percent of memantine bound melanin was calculated. The results showed 41.44%, 19.75%, and 10.68% drug bound to melanin at the concentrations of 0.01277, 0.1277, and 0.5319 mcmol/ml melanin. Insignificant binding to melanin was found at 12.77 and 38.30 mcmol/mg melanin. No glucose binding was observed. In conclusion, memantine binds to melanin moderately at low concentrations expected to be found at therapeutic doses.

Metabolism:

Memantine metabolites in mouse, rat, baboon, and human urine were determined using α assay. Mice were administered 80 mg/kg/day oral memantine HCl, once daily for 5 days, and urine was collected and pooled over an 8-hour period after the last dose for evaluation of urinary metabolites. The rats received a single memantine HCl dose of 80 mg/kg, and urine was collected over a period of 8 hours after dosing. The baboons were administered 8 mg/kg/day oral memantine HCl once daily for 14 days, and urine was collected over 24 hours after the last dose. Human volunteers were administered 5 mg memantine HCl t.i.d. (15 mg/day) for 19 days, and urine was collected over 24 hours after the last dose (day 19-20).

The major metabolites identified in mouse urine were MRZ 2/373 (3-hydroxymethyl-metabolite, 14.5% relative to memantine content), MRZ 2/374 (4/8-hydroxy-regio-isomers, 8.5%), and total

MRZ 2/525 (free and conjugated N-hydroxy-metabolite, 6.6%), and minor metabolites are analogues of MRZ 2/564 (1-amino-2-hydroxy-3,5-dimethyl-adamantane HCl, 2 isomers, 5.6%) and MRZ 2/677 (1-amino-2-hydroxy-5,7-dimethyl-adamantane HCl) or (1-amino-3,5-dimethyl-9-hydroxy-adamantane HCl, 5.6%). The major metabolites in the rat urine were MRZ 2/373 (1-amino-3-hydroxymethyl-5-methyl-adamantane HCl, 294%), MRZ 2/375 (1-amino-3-carboxy-5-methyl-adamantane HCl, 54%), MRZ 2/374 (isomeric mixture of 1-amino-3,5-dimethyl-4/8-hydroxy-adamantane HCl, 48%), and MRZ 2/325 (1-N-(3,5-dimethyl)-gludantan, 18.6%). The major metabolites in the baboon urine were MRZ 2/529 (II, 1-nitro-7-hydroxy-3,5-dimethyl-adamantane, 505.6%), MRZ 2/374 (4/8-hydroxy-regio-isomers, 188%), MRZ 2/373 (3-hydroxymethyl-metabolite, 119%), MRZ 2/371 (1-amino-3,5-dimethyl-7-hydroxy-adamantane HCl, 118%), MRZ 2/529 (1-nitro-7-hydroxy-3,5-dimethyl-adamantane, 67%), and MRZ 2/524 (45%). The major metabolites in the human urine were MRZ 2/325 (1-N-(3,5-dimethyl)-gludantan, 19%), MRZ 2/374 (4/8-hydroxy-regio-isomers, 18%), MRZ 2/524 (13%), and MRZ 2/525 (total N-hydroxy-memantine, 3%).

MRZ 2/374 was found in high concentration in all 5 species including humans, MRZ 2/373 was found in all nonhuman species and at a lower concentration in humans, and MRZ 2/375 was found in the rodent (mouse and rat) urine but not detected in human urine. Overall, all metabolites detected in the human urine were found in rats and baboons. Mice lacked MRZ 2/529 and the hydroxylated metabolite of an unidentified metabolite found in baboons and humans. The major differences in urinary memantine metabolite profile among species were the presence of MRZ 2/564 and MRZ 2/677 in rodents only, and the absence of specific isomers of MRZ 2/529 in mice or rats. MRZ 2/529 concentration was high in baboon and comprised only a minor proportion of total metabolites in human urine, and was absent in the rat and mouse urine. The remaining differences were related to proportion of the individual metabolites in relation to total metabolic profile.

The results of the urinary memantine metabolite measurements are presented in the following tables:

% Content Relative to Memantine

Code	Mice	Rat 1	Rat 2	Baboons	Humans
MRZ 2/145 (memantine)	100.0	-	-	-	-
MRZ 2/544 (N-formyl-1-amino-3,5-dimethyl-adamantane)	0.005	0.01	0.02	0.23	0.91
MRZ 2/84 (N-acetyl-1-amino-3,5-dimethyl-adamantane)	0.001	0.02	0.23	0.01	<0.01
MRZ 2/325 (1-N-(3,5-dimethyl)-gludantan)	1.33	18.59	0.49	1.80	18.85
MRZ 2/525 (N-hydroxy-1-amino-3,5-dimethyl-adamantane HCl)	1.68	1.08	nd	0.01	0.39
MRZ 2/525*	6.58	2.27	0.66	30.83	2.80
MRZ 2/371 (1-amino-3,5-dimethyl-7-hydroxy-adamantane HCl)	1.93	6.85	4.62	117.93	0.89
MRZ 2/373 (1-amino-3-hydroxymethyl-5-methyl-adamantane HCl)	14.53	294.31	210.60	119.09	0.51
MRZ 2/375 (1-amino-3-carboxy-5-methyl-adamantane HCl)	0.28	54.30	24.78	12.72	nd
MRZ 2/374** (isomeric mixture of 1-amino-3,5-dimethyl-4/8-hydroxy-adamantane HCl)	8.48	48.19	42.11	187.84	18.09

MRZ 2/564*** (1-amino-2-hydroxy-3,5-dimethyl-adamantane HCl)	5.61	0.77	1.42	-	
MRZ 2/677 (1-amino-2-hydroxy-5,7-dimethyl-adamantane HCl) or (1-amino-3,5-dimethyl-9-hydroxy-adamantane HCl)	5.56	0.50	0.21		
MRZ 2/523	0.09	0.04	0.03	1.19	0.17
MRZ 2/524	2.93	0.50	nd	44.57	13.01
MRZ 2/529**** (1-nitro-7-hydroxy-3,5-dimethyl-adamantane)	3.10	nd	nd	66.91	0.17
MRZ 2/529 (I)	-	-	-	1.91	1.08
MRZ 2/529 (II)	-	3.36	2.21	505.59	1.53
MRZ 2/529 (III)	-	1.63	1.27	-	-
MRZ 2/169 (N-methyl-1-amino-3,5-dimethyl-7-hydroxy-adamantane HCl)	nd	-	-	-	-
MRZ 2/X*****	-	-	-	26.83	0.80

*Total (free + conjugated) N-hydroxy-memantine

**Sum of 4- and 8-hydroxy regio-isomeric metabolites

***Sum of isomeric peaks

****Sum of MRZ 2/529-derived isomers 1-3

*****Unidentified, presumably hydroxylated metabolite

nd: not detected

% Content Relative to Memantine + Total Metabolites

Code	Mice	Rat 1	Rat 2	Baboons	Humans
MRZ 2/145	68.76	18.8	25.73	8.27	63.02
MRZ 2/544	0.004	<0.01	<0.01	0.02	0.57
MRZ 2/84	0.001	<0.01	0.07	<0.01	<0.01
MRZ 2/325	0.91	3.50	0.13	0.15	11.88
MRZ 2/525	1.16	0.21	nd	<0.01	0.25
MRZ 2/525*	4.53	0.43	0.17	2.55	1.77
MRZ 2/371	1.33	1.29	1.19	9.76	0.56
MRZ 2/373	9.99	55.39	54.18	9.85	0.32
MRZ 2/375	0.19	10.22	6.37	1.05	nd
MRZ 2/374**	5.83	9.07	10.83	15.55	11.36
MRZ 2/564***	3.86	0.15	0.37	-	-
MRZ 2/677	0.38	0.10	0.05	-	-
MRZ 2/523	0.06	<0.01	<0.01	0.10	0.10
MRZ 2/524	2.02	0.09	nd	3.79	8.26
MRZ 2/529****	2.13	nd	nd	5.54	nd
MRZ 2/529 (I)	-	-	-	0.16	0.68
MRZ 2/529(II)	-	0.63	0.57	41.8	0.97
MRZ 2/529(III)	-	0.31	0.33	-	-
MRZ 2/169	nd	-	-	-	-
MRZ 2/Z*****	-	-	-	2.22	0.50

*Total (free + conjugated) N-hydroxy-memantine

**Sum of 4- and 8-hydroxy regio-isomeric metabolites

***Sum of isomeric peaks

****Sum of MRZ 2/529-derived isomers 1-3

***** unidentified, presumably hydroxylated metabolite

nd: not detected

An additional study was conducted to reevaluate and quantify the N-nitroso-deaminated (MRZ 2/524) and 1-nitro-deaminated (MRZ 2/523) metabolites in the samples from the previous study

using acidic extraction, because the previous methodology using alkaline extraction resulted in degradation of N-hydroxy metabolite to these components. The results showed lower concentrations of MRZ 2/524 in mouse (9363 ng/ml), rat (499.5 and 1645 ng/ml in 2 samples), baboon (3968 ng/ml), and human (380 ng/ml) urine. The results showed lower concentrations of MRZ 2/523 in mouse (289 ng/ml), rat (132 and 51 ng/ml), baboon (106 ng/ml), and human (5 ng/ml) urine.

The biotransformation of memantine in the mouse, rabbit, dog, baboon, and humans was studied in another comparative metabolite screening program. Male NMRI strain mice received 20 mg/kg (50 uCi/animal), and male rabbits, Beagle dogs and baboons received 5 mg/kg (100, 600, and 400 uCi/animal, respectively) ^{14}C -memantine by oral gavage in a single dose. Blood, urine, and feces were collected at appropriate intervals for determination of pharmacokinetic parameters and metabolite pattern. Human samples were obtained from a previous clinical study (Preliminary pharmacokinetic investigations with ^{14}C -memantine in healthy volunteers. Report for Merz + Co. GmbH & Co., September 1983). The results are presented in the following table (reproduced from the original NDA submission):

**Proportions of Memantine, Glucuronic Acid Conjugates and Sulphuric Acid Conjugates
in the Urine after Oral Administration of ^{14}C -Memantine
in the Mouse, Rabbit, Dog, Baboon, and Man**

Species/time after dosing	% Memantine	% Glucuronides	% Sulphate
Mouse 1 0-24 h	38	10	<2
24-48 h	27	nd	nd
Mouse 2 0-24 h	38	6	<2
24-48 h	23	nd	nd
Rabbit 1 0-24 h	18	8	5
Rabbit 2 0-24 h	12	14	5
Dog 1 0-24 h	10	8	5
24-48 h	24	nd	nd
Dog 2 0-24 h	12	15	5
24-48 h	30	nd	nd
Baboon 1 0-24 h	10	25	4
24-48 h	6	nd	nd
Baboon 2 0-24 h	8	25	10
24-48 h	6	nd	nd
Man 0-6 h	ca. 55	ca. 36	
48-72 h	ca. 84	ca. 15	
96-120 h	>95		

Nd = not determined

The potential effects of memantine HCl and structural analogs of memantine, in comparison to effects of amantadine HCl on hepatic microsomal metabolism of aminopyrine (N-demethylase activity) was studied in male rats. Amantadine decreased the formation of formaldehyde from aminopyrine *in vitro*, whereas memantine (11.84-13.59 mg/kg/day) had no effect on the N-demethylase activity in microsomes prepared from rats treated for 3 days.

Excretion:

A repeated dose excretion study was conducted in mice administered oral memantine (10 mg/kg) three times daily with unlabeled drug for 7 days, followed by one ^{14}C -labeled oral memantine

dose on the 8th day and unlabeled memantine for the remaining doses on the 8th and 9th days. Radioactivity was measured in the expired air, urine, feces, sweat, and tissues. The results are presented in the following table:

Sample	% radioactive dose (22 nd administration)
Urine and feces	
0-9 hours	48.2%
9-25 hours	27.5%
25-48 hours	17.5%
Washing water and swabs (0-48 hours)	7.8%
Total	101.0%
Respiratory air + volatile components	
In absorption tower 1 (acidic)	<0.1%
In absorption tower 2 (alkaline)	<0.1%
Residual animal body	1.0%

The results showed nearly complete renal and fecal excretion of oral memantine within 48 hours of dosing in mice. Exhaled and tissue memantine levels were below the level of detection (<0.1% and <1.0%, respectively).

Male mice were administered a single dose of 5 mg/kg memantine hydrochloride (10 mCi) by oral gavage, miniature pigs were administered a single dose of 5 mg/kg (200 mCi) by oral gavage, and baboons were administered a single dose by oral gavage, on day 1, twice daily on days 2-6, and a final single dose of 5 mg/kg (100 mCi) on day 7. Blood (pigs, baboons), urine (mice, pigs, baboons), feces (mice, pigs, baboons), and tissue (baboons) samples were collected at appropriate timepoints. The results showed approximately 57%-76% renal excretion and 13%-18% fecal excretion in the first 24 hours after dosing (cumulative), and 65%-88% renal and 15%-28% fecal excretion in the first 48 hours after dosing (cumulative) for a total 48 hour excretion of 70%-93% over 24 hours and 84%-106% over 48 hours in the mice. Cumulative renal and fecal excretion combined were 31%-50% in the first 24 hours and 77%-89% in the first 48 hours after dosing in the baboon. In the miniature pig, urinary excretion accounted for 83%-85% in the first 24 hours and 89%-94% dose in the first 48 hours after dosing, the feces fraction was 2% in the first 24 hours and 5% in the first 48 hours after dosing, and total excretion in urine and feces was 85%-86% over 24 hours and 94%-99% over 48 hours after dosing.

In another comparative pharmacokinetics and metabolism study, renal and fecal excretion of ¹⁴C-labeled memantine was nearly complete at 48 hours after dosing in the mouse, rabbit and dog, but only 59-76% radioactivity was excreted at 72 hours after dosing in the baboon. In comparison, 47% orally administered ¹⁴C-memantine was excreted at 72 hours after administration in the human study (see Preliminary pharmacokinetic investigations with ¹⁴C-memantine in healthy volunteers. Report for Merz + Co. GmbH & Co., September 1983). Excretion was predominantly by the renal route in all species evaluated.

In male Sprague Dawley rats administered ¹⁴C-labeled memantine HCl by oral gavage at doses from 0.5-12 mg/kg, the radioactivity was nearly completely eliminated by 24 hours after dosing. The ratio of radioactivity recovered in urine and feces was approximately 4:1, regardless of dose and number of repeated daily doses from 1-10.

Urinary excretion in pregnant rabbits was 10.14% at 0-6 hours, 76.71% at 6-24 hours, 2.07% at 24-48 hours, and 0.35% at 48-72 hours after dosing, for a total of 89.27% during the period from 0-72 hours after dosing.

The saturation of the enterohepatic circulation during long-term use was investigated in another excretion study in mice administered ¹⁴C-labeled memantine by single and repeated oral doses of 10 mg/kg. Radioactivity measurements in the urine, feces, and bile after 1, 10, and 27 doses (1, 3 and 9 days at 3 doses/day) showed approximately 70% excretion by the renal and fecal routes combined. Radioactivity in bile accounted for <4% with no difference in proportion in the bile after the single dose and the 27th dose. Therefore, no saturation was found in mice, under the conditions of this study.

IV. GENERAL TOXICOLOGY:

Study title: 14-day dose-range-finding study of memantine HCl in B6C3F1 mice by administration in the diet (to determine the palatability of dietary treatment levels for a 13-week maximum tolerated dose-level (MTD) study)

Key study findings:

- Dose-related reduction in body weight gain in males and females at 120 and 240 mg/kg/day
- Food consumption increased in males (dose-related) and decreased in females (no dose-relationship) at all doses from 60-240 mg/kg/day
- No treatment-related deaths, clinical signs, organ weight changes and gross pathology findings, histopathology examination of eyes negative for toxicity
- 5, 25, and 125 mg/kg/day selected for the 13-week oral toxicity study in mice, although the doses of 5, 20, 80, 160, and 320 mg/kg/day were ultimately evaluated in the 13-week study

Study no: 7195/92

Volume # 22, and page # 114

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 8825, radiolabel Not applicable, and % purity 99.8%

Formulation/vehicle: Test article admixture in feed

Methods (unique aspects):

Dosing:

Species/strain: B6C3F1 CrlBR mouse _____

#/sex/group or time point (main study): 5/sex/group

Satellite groups used for toxicokinetics or recovery: None

Age: 27 days

Weight: 13.2-17.0 g

Doses in administered units: 0, 60, 120, 240 mg/kg/day

Route, form, volume, and infusion rate: Admixture of test article in feed (Standard diet). Homogeneity of test article in vehicle confirmed by sampling at baseline, and after 1st week of dosing from the top, middle and bottom of feed bucket

Observations and times:

Clinical signs: Daily

Body weights: Baseline and weekly

Food consumption: Baseline and weekly

Ophthalmoscopy: Not done

EKG: Not done

Hematology: Not done

Clinical chemistry: Not done

Urinalysis: Not done

Gross pathology: At end of 14-day dosing period: adrenals, eyes, optic nerve, Harderian gland, kidneys, liver, lungs, bronchi, mesenteric and submaxillaris lymph nodes, spleen, thymus, thyroids, parathyroids

Organs weighed: Adrenals, brain, kidneys, spleen, epididymides, ovaries, thymus, uterus, pituitary, testicles, thyroids

Histopathology: Kidneys only; remaining organs were preserved in 10% buffered formalin for future histology

Toxicokinetics: Not done

Other: None

Results:

Mortality: No deaths

Clinical signs: No treatment-related clinical signs

Body weights: The results of the body weight change measurements are presented in the following table:

Percent Change in Body Weights (from Baseline) in Mice Administered Memantine HCl (Dietary) for 14 Days

Study Day	0 mg/kg/day	60 mg/kg/day	120 mg/kg/day	240 mg/kg/day
Males				
7	+7.8%	+9%	+2.1%	No change
14	+15.2%	+14.4%	+7.3%	+4.2%
Females				
7	-2.4%	+1.8%	-1.2%	-3.6%
14	+1.8%	+10.1%	+5.4%	-3.0%

Food consumption: Dose related increase in males, decreased in females without dose relationship; results are presented in the following table:

Changes in Food Consumption (Compared to Controls) in Mice Administered Memantine HCl (Dietary) for 14 Days

Dose (mg/kg/day)	Sex	Week 1	Week 2
60	Male	+18%	+40%
120	Male	+20%	+52%
240	Male	+49%	+59%
60	Female	-23%	-14%
120	Female	-10%	-9%
240	Female	-16%	-29%

Ophthalmoscopy: Not done

Electrocardiography: Not done

Hematology: Not done

Clinical chemistry: Not done

Urinalysis: Not done

Organ weights: Slight decrease in HD males in absolute spleen and kidney weights, relative organ weights within range of historical controls, therefore organ weight changes attributed to overall changes in body weights

Gross pathology: No treatment-related effects

Histopathology: No treatment-related effects in kidneys,

Toxicokinetics: Not done

Study title: 13-Week Dose-Range Finding Study of Memantine HCl in B6C3F1 Mice by Administration in the Diet (To Determine the Maximum Tolerated Dose-Level for a Long-Term Feeding Study in Mice): includes Supplementary histopathology report, Addendum No. 1. — Study 7196/92, Vol. 25, p. 1

Key study findings:

- Memantine intake comparable to intended doses of 5, 20, 80, 160, and 320 mg/kg/day
- Mortality in 6/20 mice at 320 mg/kg/day, in the 5th, 10th and 11th weeks of treatment
- Reduced body weight gain at 80, 160, and 320 mg/kg/day when compared to controls, more pronounced in the males (M, 10%, 14% and 21% lower than control gain, respectively) than in the females (F, 6%, 11%, 12%, respectively)
- Loss of retinal blood vessels in 2/10M and 2/10F at 160 mg/kg/day, 3/10M at 320 mg/kg/day
- Increased platelets, total protein, serum albumin, and albumin-globulin ratio, beta-globulin, and decreased alpha1- and alpha2- globulin in males; decreased urine specific gravity in females at 320 mg/kg/day
- Endothelial vacuolization and pyknosis of superficial epithelial cells of the corneal epithelium in 3/10 females, and vacuolization of the tubular epithelium of the kidney in 1/10 females at 160 mg/kg/day, and endothelial vacuolisation, pyknosis of superficial epithelial cells of the corneal epithelium, edema of the substantia propria, superficial edema of the epithelium, endothelial vacuolization, focal epithelial defect, different thickness of epithelium, thickening of Descemet's membrane in 10/10 males, vacuolization of the tubular epithelium of the kidney in 2/10 females, focal vacuolization of the tubular epithelium in the tubulus contortus, focal necrosis of the tubular epithelium of the kidney in 7/10 males at 320 mg/kg/day
- MTD 80 mg/kg/day (19X the MRHD of 20 mg/d in a 60 kg patient on a BSA basis) in the male and female mice, based on decreased body weight gain, loss of retinal blood vessels, and eye and kidney histopathology at higher doses of 160 and 320 mg/kg/day (39X-78X the MRHD)

Study no: — No. 7196/92

Volume # 23, and page # 1, and Volume #25, p. 1.

Conducting laboratory and location: _____

Date of study initiation: April 13, 1992

GLP compliance: yes (x) no ()

QA report: yes (x) no ()

Drug Memantine HCl, lot # Groups 1-4: R 8825, Groups 5-7: R 7206, **radiolabel** Not applicable, **and % purity** Groups 1-4: 100.5%, Groups 5-7: 99.7%

Formulation/vehicle: Admixture of test article in standard diet _____); samples taken for analysis of homogeneity from 3 levels in the feed bucket at start of study, at 7 days, and in week 13

Methods (unique aspects):

Dosing:

Species/strain: B6C3F1 CrIBR Mice _____

#/sex/group or time point (main study): 10/sex/group

Satellite groups used for toxicokinetics or recovery: 6/sex/group for PK study

Age: Groups 1-4: 30-31 days (males), 41-42 days (females), Groups 5-7: 26-27 days (males), 34-35 days (females)

Weight: Groups 1-4: 15.1-18.9 g, Groups 5-7: 15.2-18.3 g

Doses in administered units: 0 (diet only, Groups 1 and 5), 5 (Group 2), 20 (Group 3), 80 (Group 4), 160 (Group 6), 320 (Group 7) mg/kg/day; the doses were selected based on the results of a 14-day dose-range-finding study (_____ No. 7195/92), a second feed-only control group (Group 5) was evaluated with the 160 and 320 mg/kg/day groups (Groups 6 and 7)

Route, form, volume, and infusion rate: Oral in the diet

Observations and times:

Clinical signs: Daily

Body weights: Baseline and Weekly

Food consumption: Baseline and Weekly

Ophthalmoscopy: Baseline and during Week 12

Auditory Function: Prior to sacrifice in Week 13

Dentition: Prior to sacrifice in Week 13

EKG: Not done

Hematology: 16 hours after withdrawal of food and test article in week 13

Clinical chemistry: 16 hours after withdrawal of food and test article in week 13

Urinalysis: Week 13, for 16 hours in an _____ funnel cage before hematology and clinical chemistry blood withdrawals

Bone Marrow: Week 13; myeloid and erythroid precursors counted, myeloid:erythroid ratio calculated

Gross pathology: Week 13

Organs weighed: Week 13: see under Histopathology Inventory, below

Histopathology: Week 13: see under Histopathology Inventory, below

Toxicokinetics: Blood samples (0.25 ml) from satellite groups, dosing days 40 and 85

Results:

Mortality: The deaths are presented in the following table:

Group	#Deaths	Test Day	Related to Test Article
1 (Control)	1F	88	-
2 (5 mg/kg/day)	1M	87	Unlikely
3 (20 mg/kg/day)	-	-	-
4 (80 mg/kg/day)	1F	86	Unlikely
5 (Control)	-	-	-
6 (160 mg/kg/day)	-	-	-
7 (320 mg/kg/day)	5M, 1F	85, 74, 85, 85, 72, 37	5 Likely, 1 Unlikely

Clinical signs: No treatment-related effects

Body weights: Dose-related decrease in body weight gain and body weight when compared to control values in the male and female mice, more pronounced in the males. The differences in body weights were statistically significant at 80, 160, and 320 mg/kg/day. The changes in body weight gain and body weights compared to control values for the entire treatment period are presented in the following table:

Group	Body Weight Gain in %		Difference in BWG % from Control %*		Body Weight Difference from Control in %*	
	Males	Females	Males	Females	Males	Females
1 (Control)	26%	31%	-	-	-	-
2 (5 mg/kg/day)	27%	34%	1%	3%	-0.7%	1.6%
3 (20 mg/kg/day)	27%	29%	-1%	-2%	1.5%	-3.6%
4 (80 mg/kg/day)	16%	25%	-10%	-6%	-5.2%	-5.2%
5 (Control)	34%	45%	-	-	-	-
6 (160 mg/kg/day)	20%	34%	-14%	-11%	-9.0%	-10.3%
7 (320 mg/kg/day)	-13%	33%	-21%	-12%	-31.0%	-11.5%

*Groups 2-4 compared to Control Group 1, Groups 6-7 compared to Control Group 5

Food consumption: Statistically significant difference in food consumption compared to control values at 160 (males, -22% and -27% in weeks 8 and 9, respectively) and 320 (males, increased 29%, 34%, and 32%, and decreased 32% in weeks 6, 8, 9, and 10, respectively) mg/kg/day. The mean intake of test article in the males was 4.70, 18.68, 76.77, 147.82, and 331.48 mg/kg in the 5, 20, 80, 160, and 320 mg/kg/day groups, respectively. The mean intake of test article in the females was 4.74, 19.28, 75.93, 153.55, and 310.99 mg/kg in the 6, 20, 80, 160, and 320 mg/kg/day groups, respectively.

Ophthalmoscopy: Retinal blood vessel loss in 2M and 2F at 160 mg/kg/day, and in 3M at 320 mg/kg/day.

Auditory Function: No treatment-related effects

Dentition: No treatment-related effects

Electrocardiography: Not done

Hematology: Slight, statistically significant increase (15%) in platelets in the males at 320 mg/kg/day

Clinical chemistry: Slight, statistically significant increase in total protein (11%), serum albumin (25%), and albumin-globulin ratio (37%), increased beta-globulin (25%), decreased alpha1- (40%) and alpha2- (20%) globulin in the males at 320 mg/kg/day

Urinalysis: Slight, statistically significant decrease in specific gravity (1%) in the females at 320 mg/kg/day

Bone Marrow: No treatment-related effects on myeloid:erythroid ratio, statistically significant increases from control values (0.6:1 and 0.9:1) at 20 (50%) and 80 (67%) mg/kg/day (0.7:1 – 1.3:1) within historical control ratios of 0.8:1 – 2.5:1.

Organ weights:

5-80 mg/kg/day: no treatment-related effects

160 mg/kg/day: Decreased relative and absolute liver (4% and 15%, respectively) and spleen (20% and 29%, respectively) weights in the males, decreased relative and absolute liver (7% and 15%, respectively) and spleen (18% and 20%, respectively) weights in the females, increased relative kidney (15%) weight in the males, and decreased relative and absolute heart weight (23% and 29%, respectively) in the females; only relative kidney weight and relative and absolute heart weight differences statistically significant

320 mg/kg/day: Decreased relative and absolute heart (23% and 43%, respectively), liver (27% and 46%, respectively), spleen (47% and 57%, respectively), kidney (8% and 35%, respectively) and epididymides (8% and 37%-42% [l and r]) weights, and increased relative brain (51%) weights in the males, and decreased relative and absolute heart (12% and 11%, respectively), liver (5% and 15%, respectively) and spleen (24% and 30%, respectively) weights in the females; only liver weight and brain weight changes were statistically significant

Gross pathology: No treatment-related effects

Histopathology:

5-80 mg/kg/day: no treatment-related effects

160 mg/kg/day: Endothelial vacuolization, pyknosis of superficial epithelial cells of the corneal epithelium in 3/10 females, vacuolization of the tubular epithelium of the kidney in 1/10 females

320 mg/kg/day: Endothelial vacuolization, pyknosis of superficial epithelial cells of the corneal epithelium, edema of the substantia propria, superficial edema of the epithelium, endothelial vacuolization, focal epithelial defect, different thickness of epithelium, thickening of Descemet's membrane in 10/10 males, vacuolization of the tubular epithelium of the kidney in 2/10 females, focal vacuolization of the tubular epithelium in the tubulus contortus, focal necrosis of the tubular epithelium of the kidney in 7/10 males

Toxicokinetics: The results of the plasma Memantine analysis are presented in the following table:

Plasma Memantine Levels in Mice Administered Memantine HCl in the Diet (ng/ml)*

Group (dose)	Test Day 40		Test Day 85	
	Males	Females	Males	Females
1 (Control)	Not Detected	Not Detected	Not Detected	Not Detected
2 (5 mg/kg/day)	18.5	10.8	11.1	7.9
3 (20 mg/kg/day)	33.8	12.1	55.4	30.0
4 (80 mg/kg/day)	129	56.3	259	125
5 (Control)	Not Detected	Not Detected	Not Detected	Not Detected
6 (160 mg/kg/day)	317	157	463	180
7 (320 mg/kg/day)	766	374	758	407

*Pooled samples, n=6/sex/dose

Study title: A repeated dose toxicity study of SUN Y7017 by dietary administration for 6 weeks and followed by a 4-week withdrawal period in Long Evans rats (a comparative toxicity study to SD rats)

Key study findings:

- No meaningful differences in toxicity by SUN Y7017 between pigmented (Long Evans) and albino (Sprague Dawley) rats
- Deaths in 5/16 rats at high dose (160 mg/kg/d) in each species
- Clinical signs at 160 mg/kg/d: hyperactivity, jumping, aggressiveness, biting, tremors, emaciation, prolapse of penis, piloerection, staggering, ptosis, soiled perinasal region, and self-biting, persisting 1 week to 10 days after drug withdrawal
- Dose-related reduced body weights at all doses throughout dosing, no species differences
- Food consumption reduced without species differences at all doses throughout treatment
- Test article intake confirmed at slightly below the intended doses in both species
- No ophthalmoscopy abnormalities in anterior segment, ocular media, and fundus either species (HD rats were not evaluated)
- Hematology: dose-related decreased platelets, leukocytes and lymphocytes in both species, at highest dose evaluated (80 mg/kg/day)
- Species differences in treatment-related clinical chemistry effects: decreased BUN and ALT and increased A/G ratio in LE rats, and increased total protein and albumin in the SD rats
- Dose-related decreased urinary pH and increased specific gravity at 80 and 160 mg/kg/day in both species
- Organ weight changes more evident (LD and MD) in pigmented than in albino rats (MD only) (HD not evaluated): Decreased absolute spleen, increased relative kidney, brain, adrenal, testes and lung weights in both species; Decreased absolute and relative liver and heart weights, decreased relative spleen weight in pigmented rats; increased absolute kidney weight and relative liver weight
- Gross pathology abnormalities were observed in high dose rats only: dry subcutaneous tissue, decreased adipose tissue, enlarged adrenals, small thymus, mesenteric lymph nodes, testes, prostate, and seminal vesicles, and dark lung at end of treatment in both species; At end of recovery, spleen enlarged in pigmented rats and small in albino rats, thymus small in the albinos and prostate and seminal vesicles small in pigmented rats, both species showed small testes and epididymides
- No treatment-related effects were observed in the histopathology examination in either species
- Doses studied approximately 19X-78X MRHD (20 mg) in a 60 kg patient, BSA basis
- NOAEL not determined

Study no: SR0004

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Conducting laboratory and location:

Date of study initiation: May 31, 2000

GLP compliance: yes (x [Japan]) no ()

QA report: yes (x) no ()

Drug SUN Y7017 (SUNTORY Ltd.), lot # 1798102, **radiolabel** Not applicable, and **% purity** 99.2%

Formulation/vehicle: Test article admixture in powder diet — , homogeneity and stability confirmed

Methods (unique aspects):

Dosing:

Species/strain: Male Crj:CD(SD) (pigmented) rats and male Kwl: Long Evans rats
#/sex/group or time point (main study): 6, 8, 8, and 16 males at 0, 40, 80, and 160 mg/kg/day, respectively

Satellite groups used for toxicokinetics or recovery: Recovery groups of 6, 8, 8, and 16 males at 0, 40, 80, and 160 mg/kg/day, respectively, necropsied after 4-week recovery period

Age: 7 weeks

Weight: 171.8-223.0 g Long Evans rats and 252.6-278.2 g Sprague Dawley rats

Doses in administered units: 0, 40, 80, and 160 mg/kg/day

Route, form, volume, and infusion rate: Oral by admixture in the diet, continuous *ad libitum* administration for 6 weeks

Observations and times:

Clinical signs: Daily throughout treatment and recovery

Body weights: 3X weekly during treatment, Daily during 1st week of recovery, then 2X weekly until necropsy

Food consumption: Baseline, 2 3-day periods each week during treatment, every 3-4 days during recovery period

Test article intake: Weekly (test article concentration in diet X mean food consumption / mean body weight)

Ophthalmoscopy: Baseline and Week 6 of treatment (LD and MD animals only)

EKG: Not done

Hematology: End of treatment, 40 and 80 mg/kg/day groups only

Clinical chemistry: End of treatment

Urinalysis: Week 6 of treatment

Gross pathology: End of treatment Week 6: external and internal organs

Organs weighed: End of treatment Week 6: brain, thymus, heart, lungs, bronchi, liver, kidneys, spleen, adrenals, testes

Histopathology: End of treatment Week 6: brain, thymus, heart, lungs, bronchi, liver, kidneys, spleen, adrenals, submandibular gland, epididymides, skeletal muscle, pancreas, stomach, duodenum, ileum, colon, mesenteric lymph nodes, pituitary gland, thyroid, parathyroid, tongue, esophagus, trachea, urinary bladder, prostate, seminal vesicles, mammary glands, spinal cord, sciatic nerve, thoracic aorta, skin, sternum, femur including bone marrow, eyes, optic nerves, Harderian gland

Toxicokinetics: Not done

Other: None

Results:

Mortality: LE (pigmented) rats: 5 deaths at 160 mg/kg/day (1 on treatment Day 33, 2 on treatment Day 41, and 2 during recovery period days 11 and 24)

SD (albino) rats: 5 deaths at 160 mg/kg/day (1 each on treatment Days 34, 37, 38, 39, and 41)

Clinical signs: No signs at 40 and 80 mg/kg/day in either species;

In the rats that died (at 160 mg/kg/day), hyperactivity, jumping, aggressiveness, biting, tremors, emaciation, prolapse of penis, piloerection, staggering, ptosis, soiled perinasal region, and self-biting were observed;

In the rats that survived, hyperactivity, aggressiveness, soiled perinasal region, piloerection, tremor, prolapsed penis, and emaciation were observed throughout treatment at the high dose;

During the recovery period, self-biting, bleeding from wounds, hyperactivity, and aggressiveness, indicating withdrawal were observed in 6-7/13 LE rats; in the recovery SD rats, no signs of withdrawal were observed, although hyperactivity, aggressiveness, prolapsed penis, piloerection and emaciation were shown for the first 10 recovery days

Body weights: LE (pigmented) rats: Reduced body weight throughout treatment at 40 (12% at end of study), 80 (18%, end of study), and from treatment Week 1 to end of treatment at 160 mg/kg/day (37%, end of study) compared to controls, increased body weights from recovery day 3 to end of recovery at 40 and 80 mg/kg/day and in the rats not showing biting behavior, body weights remained decreased during recovery in the rats showing biting behavior

SD (albino) rats: Reduced body weights throughout treatment at 40 (9% at end of treatment), 80 (15%), and 160 mg/kg/day (50%) compared to controls; increased body weights from recovery Day 3 to end of recovery at 40, 80, and 160 mg/kg/day

Food consumption: LE (pigmented) rats: Reduced at 40, 80, and 160 mg/kg/day throughout treatment, increased from recovery Day 4 until end of recovery

SD (albino) rats: Reduced at 40, 80, and 160 mg/kg/day, increased from recovery Day 4 through end of recovery

Test article intake: Slightly below intended doses of 40, 80, and 160 mg/kg/day, at 38.5, 75.9, and 150.1 mg/kg/day in the LE (pigmented) rats and 37.9, 75.4, and 140.6 mg/kg/day in the SD (albino) rats

Ophthalmoscopy: No abnormalities observed in the anterior segment, ocular media, and fundus at 40 and 80 mg/kg/day in either species (HD rats not evaluated)

Electrocardiography: Not done

Hematology: LE (pigmented) rats: Decreased platelets (11%), leukocytes (23%), and lymphocytes (26%) at 80 mg/kg/day (HD group not evaluated)

SD (albino) rats: Decreased platelets (13%), leukocytes (35%), and lymphocytes (38%) at 80 mg/kg/day (HD group not evaluated)

Clinical chemistry: LE (pigmented) rats: Decreased BUN at 40 (16%) and 80 (16%) mg/kg/day, decreased ALT (15%) and increased A/G (10%) ratio at 80 mg/kg/day (HD rats not evaluated)

SD (albino) rats: Increased total protein (4%) and albumin (6%) at 80 mg/kg/day (HD rats not evaluated)

Urinalysis: LE (pigmented) rats: Decreased pH at 80 (8%) and 160 (22%) mg/kg/day, increased specific gravity at 80 (1%) and 160 (1%) mg/kg/day

SD (albino) rats: Decreased pH at 80 (14%) and 160 (21%) mg/kg/day, increased specific gravity at 80 (1%) and 160 (2%) mg/kg/day

Organ weights: LE (pigmented) rats: LD and MD only were evaluated: Decreased absolute (15% in LD, 21% in MD) and relative (5%, LD) liver, absolute (14% in LD, 22% in MD) and relative (9%, MD) spleen, increased relative brain (10% in LD, 19% in