

GENERIC DRUG- memantine hydrochloride tablets tablet
Ningbo Shouzheng Medicinal Research Co., Ltd

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HIGHLIGHTS OF PRESCRIBING INFORMATION

*Sections or subsections omitted from the Full Prescribing Information are not listed.

1 INDICATIONS AND USAGE

Memantine Hydrochloride Tablets USP is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

2 DOSAGE AND ADMINISTRATION

The recommended starting dose of Memantine Hydrochloride Tablet is 5 mg once daily. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice daily), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice daily). The minimum recommended interval between dose increases is one week. The dosage shown to be effective in controlled clinical trials is 20 mg/day.

Memantine Hydrochloride Tablet can be taken with or without food. If a patient misses a single dose of Memantine Hydrochloride Tablet, that patient should not double up on the next dose. The next dose should be taken as scheduled.

If a patient fails to take Memantine Hydrochloride Tablet for several days, dosing may need to be resumed at lower doses and retitrated as described above.

Specific Populations

Renal Impairment

A target dose of 5 mg twice daily is recommended in patients with severe renal impairment (creatinine clearance of 5 – 29 mL/min based on the Cockcroft-Gault equation).

Hepatic Impairment

Memantine Hydrochloride Tablet should be administered with caution to patients with severe hepatic impairment [see *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Memantine Hydrochloride 5 mg tablet: round, film-coated tablets are tan, with the strength (M5) debossed on one side and V on the other.

Memantine Hydrochloride 10 mg tablet: round, film-coated tablets are gray, with the strength (M10) debossed on one side and X on the other.

4 CONTRAINDICATIONS

Memantine Hydrochloride Tablet is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Genitourinary Conditions

Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine [see Drug Interactions (7.1)] .

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Memantine hydrochloride was evaluated in eight double-blind placebo-controlled trials involving a total of 1862 dementia (Alzheimer's disease, vascular dementia) patients (940 patients treated with memantine hydrochloride and 922 patients treated with placebo) for a treatment period up to 28 weeks.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Events Leading to Discontinuation

In placebo-controlled trials in which dementia patients received doses of memantine hydrochloride Tablet up to 20 mg/day, the likelihood of discontinuation because of an adverse reaction was the same in the memantine hydrochloride group (10.1%) as in the placebo group (11.5%). No individual adverse reaction was associated with the discontinuation of treatment in 1% or more of memantine hydrochloride-treated patients and at a rate greater than placebo.

Most Common Adverse Reactions

In double-blind placebo-controlled trials involving dementia patients, the most common adverse reactions (incidence \geq 5% and higher than placebo) in patients treated with Memantine Hydrochloride were dizziness, headache, confusion and constipation. Table 1 lists all adverse reactions that occurred in at least 2% of patients treated with memantine hydrochloride and at an incidence greater than placebo.

Table 1: Adverse Reactions Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Memantine Hydrochloride and at a Higher Frequency than Placebo-treated Patients

Adverse Reaction	Placebo (N= 922) %	Memantine Hydrochloride (N= 940) %
Body as a whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral Nervous		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucination	2	3

Respiratory System		
Coughing	3	4
Dyspnea	1	2

The overall profile of adverse reactions and the incidence rates for individual adverse reactions in the subpopulation of patients with moderate to severe Alzheimer's disease were not different from the profile and incidence rates described above for the overall dementia population.

Seizures

Memantine hydrochloride has not been systematically evaluated in patients with a seizure disorder. In clinical trials of memantine hydrochloride, seizures occurred in 0.2% of patients treated with memantine hydrochloride and 0.5% of patients treated with placebo.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of memantine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include:

Blood and Lymphatic System Disorders - agranulocytosis, leukopenia (including neutropenia), pancytopenia, thrombocytopenia, thrombotic thrombocytopenic purpura.

Cardiac Disorders - cardiac failure congestive.

Gastrointestinal Disorders - pancreatitis.

Hepatobiliary Disorders – hepatitis.

Psychiatric Disorders - suicidal ideation.

Renal and Urinary Disorders - acute renal failure (including increased creatinine and renal insufficiency).

Skin Disorders - Stevens Johnson syndrome.

7 DRUG INTERACTIONS

7.1 Drugs that Make the Urine Alkaline

The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8.

Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

7.2 Use with Other N-methyl-D-aspartate (NMDA) Antagonists

The combined use of Memantine Hydrochloride with other NMDA antagonists (amantadine, ketamine,

and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of memantine hydrochloride in pregnant women.

Adverse developmental effects (decreased body weight, and skeletal ossification) were observed in the offspring of rats administered memantine during pregnancy at doses associated with minimal maternal toxicity. These doses are higher than those used in humans at the maximum recommended daily dose of memantine hydrochloride [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Oral administration of memantine (0, 2, 6, or 18 mg/kg/day) to rats during the period of organogenesis resulted in decreased skeletal ossification in fetuses at the highest dose tested. The higher no-effect dose for adverse developmental effects (6 mg/kg) is 3 times the maximum recommended human daily dose (MRHD) of memantine hydrochloride (20 mg) on a body surface area (mg/m^2) basis.

Oral administration of memantine to rabbits (0, 3, 10, or 30 mg/kg/day) during the period of organogenesis resulted in no adverse developmental effects. The highest dose tested is approximately 30 times the MRHD of memantine hydrochloride on a mg/m^2 basis.

In rats, memantine (0, 2, 6, or 18 mg/kg/day) was administered orally prior to and throughout mating and, in females, through the period of organogenesis or continuing throughout lactation to weaning. Decreased skeletal ossification in fetuses and decreased body weight in pups were observed at the highest dose tested. The higher no-effect dose for adverse developmental effects (6 mg/kg/day) is 3 times the MRHD of memantine hydrochloride on a mg/m^2 basis.

Oral administration of memantine (0, 2, 6, or 18 mg/kg/day) to rats from late gestation throughout lactation to weaning, resulted in decreased pup weights at the highest dose tested. The higher no-effect dose (6 mg/kg/day) is approximately 3 times the MRHD of memantine hydrochloride on a mg/m^2 basis.

8.2 Lactation

Risk Summary

There are no data on the presence of memantine in human milk, the effects on the breastfed infant, or the effects of memantine hydrochloride on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for memantine hydrochloride and any potential adverse effects on the breastfed infant from memantine hydrochloride or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Memantine failed to demonstrate efficacy in two 12-week controlled clinical studies of 578 pediatric patients aged 6-12 years with autism spectrum disorders (ASD), including autism, Asperger's disorder

and Pervasive Development Disorder - Not Otherwise Specified (PDD-NOS). Memantine has not been studied in pediatric patients under 6 years of age or over 12 years of age. Memantine treatment was initiated at 3 mg/day and the dose was escalated to the target dose (weight-based) by week 6. Oral doses of memantine 3, 6, 9, or 15 mg extended-release capsules were administered once daily to patients with weights < 20 kg, 20-39 kg, 40-59 kg and ≥ 60 kg, respectively.

In a randomized, 12-week double-blind, placebo-controlled parallel study (Study A) in patients with autism, there was no statistically significant difference in the Social Responsiveness Scale (SRS) total raw score between patients randomized to memantine (n=54) and those randomized to placebo (n=53). In a 12-week responder-enriched randomized withdrawal study (Study B) in 471 patients with ASD, there was no statistically significant difference in the loss of therapeutic response rates between patients randomized to remain on full-dose memantine (n=153) and those randomized to switch to placebo (n=158).

The overall risk profile of memantine in pediatric patients was generally consistent with the known risk profile in adults [see Adverse Reaction(6.1)]

In Study A, the adverse reactions in the memantine group (n=56) that were reported in at least 5% of patients and at least twice the frequency of the placebo group (N=58) are listed in Table 2:

Table 2: Study A Commonly Reported Adverse Reactions with a Frequency ≥ 5% and Twice That of Placebo

Adverse Reaction	Memantine N=56	Placebo N=58
Cough	8.9%	3.4%
Influenza	7.1%	3.4%
Rhinorrhea	5.4%	0%
Agitation	5.4%	1.7%
Discontinuations due to adverse reactions^a		
Aggression	3.6%	1.7%
Irritability	1.8%	3.4%

^a Reported adverse reactions leading to discontinuation in more than one patient in either treatment group.

The adverse reactions that were reported in at least 5% of patients in the 12-48 week open-label study to identify responders to enroll in Study B are listed in Table 3:

Table 3: 12-48 Week Open Label Lead-In study to Study B Commonly Reported Adverse Reactions with a Frequency ≥ 5%

Adverse Reaction	Memantine N=903
Headache	8.0%
Nasopharyngitis	6.3%
Pyrexia	5.8%
Irritability	5.4%
Discontinuations due to adverse reactions^a	
Irritability	1.2%
Aggression	1.0%

^a At least 1% incidence of adverse reactions leading to premature discontinuation.

In the randomized withdrawal study (Study B), the adverse reaction in patients randomized to placebo

(n=160) and reported in at least 5% of patients and at twice the frequency of the full-dose memantine treatment group (n=157) was irritability (5.0% vs 2.5%).

Juvenile Animal Study

In a study in which memantine (0, 15, 30 or 45 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days [PND] 14 through 70), delays in sexual maturation were noted in males and females at all but the lowest dose tested, and body weight was reduced at the high dose. In rats orally administered memantine as a single dose (PND 14) or three daily doses (PND 14-16), neuronal lesions were observed in several areas of the brain at all but the lowest dose tested. Adverse neurobehavioral effects (decreased auditory startle habituation) were observed at the high dose. The no-effect dose for developmental toxicity was the lowest dose tested (15 mg/kg/day).

In a second juvenile animal study, memantine (0, 1, 3, 8, 15, 30, and 45 mg/kg/day) was orally administered to male and female rats beginning on PND 7 and continuing for various periods during postnatal development. Because of early memantine-related mortality, the 30 and 45 mg/kg/day groups were terminated without further evaluation. Apoptosis or neuronal degeneration in the brain was observed on PNDs 8-17 at a dose of 15 mg/kg/day. The no-effect dose for apoptosis and neuronal degeneration was 8 mg/kg/day. In animals in which memantine (0, 1, 3, 8, or 15 mg/kg/day) was orally administered on PNDs 7-70, adverse neurobehavioral effects (increased locomotor motor activity, increased auditory startle response and decreased habituation, and deficit in learning and memory) were observed at all but the lowest dose tested. Effects on auditory startle persisted after drug discontinuation. The no-effect dose for developmental toxicity was the lowest dose tested (1 mg/kg/day).

8.5 Geriatric Use

The majority of people with Alzheimer's disease are 65 years and older. In the clinical studies of memantine hydrochloride the mean age of patients was approximately 76; over 90% of patients were 65 years and older, 60% were 75 years and older, and 12% were at or above 85 years of age. The efficacy and safety data presented in the clinical trial sections were obtained from these patients. There were no clinically meaningful differences in most adverse events reported by patient groups \geq 65 years old and $<$ 65 years old.

8.6 Renal Impairment

No dosage adjustment is needed in patients with mild or moderate renal impairment. A dosage reduction is recommended in patients with severe renal impairment [see *Dosage and Administration (2) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Memantine hydrochloride should be administered with caution to patients with severe hepatic impairment [see *Dosage and Administration (2) and Clinical Pharmacology (12.3)*].

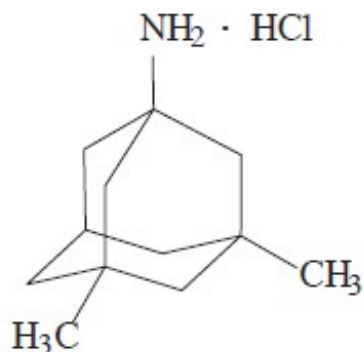
10 OVERDOSAGE

Signs and symptoms most often accompanying memantine overdosage in clinical trials and from worldwide marketing experience, alone or in combination with other drugs and/or alcohol, include agitation, asthenia, bradycardia, confusion, coma, dizziness, ECG changes, increased blood pressure, lethargy, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of memantine worldwide was 2.0 grams in a patient who took memantine in conjunction with unspecified antidiabetic medications. The patient experienced coma, diplopia, and agitation, but subsequently recovered. Fatal outcome has been very rarely reported with memantine, and the relationship to memantine was unclear.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.

11 DESCRIPTION

Memantine Hydrochloride USP is an orally active NMDA receptor antagonist. The chemical name for memantine hydrochloride is 1-amino-3,5-dimethyladamantane hydrochloride with the following structural formula:



The molecular formula is C₁₂H₂₁N•HCl and the molecular weight is 215.76. Memantine hydrochloride occurs as a fine white to off-white powder and is soluble in water.

Memantine Hydrochloride Tablets are available for oral administration as round-shaped, film-coated tablets containing 5 mg and 10 mg of memantine hydrochloride. The tablets also contain the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the following inactive ingredients are also present as components of the film coat: hypromellose, titanium dioxide, polyethylene glycol 400, and Triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels. There is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's disease.

12.2 Pharmacodynamics

Memantine showed low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine and glycine receptors and for voltage-dependent Ca²⁺, Na⁺ or K⁺ channels. Memantine also showed antagonistic effects at the 5HT₃ receptor with a potency similar to that for the NMDA receptor and blocked nicotinic acetylcholine receptors with one-sixth to one-tenth the potency.

In vitro studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil, galantamine, or tacrine.

12.3 Pharmacokinetics

Absorption

Following oral administration memantine is highly absorbed with peak concentrations reached in about 3-7 hours. Memantine has linear pharmacokinetics over the therapeutic dose range. Food has no effect on the absorption of memantine.

The remainder is converted primarily to three polar metabolites which possess minimal NMDA receptor antagonistic activity: the N-glucuronide conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine. A total of 74% of the administered dose is excreted as the sum of the parent drug and the N- glucuronide conjugate. Renal clearance involves active tubular secretion moderated by pH dependent tubular reabsorption.

Pharmacokinetics in Specific Populations

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m² basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m² basis, respectively) through 128 weeks.

Memantine produced no evidence of genotoxic potential when evaluated in the *in vitro* *S. typhimurium* or *E. coli* reverse mutation assay, an *in vitro* chromosomal aberration test in human lymphocytes, an *in vivo* cytogenetics assay for chromosome damage in rats, and the *in vivo* mouse micronucleus assay. The results were equivocal in an *in vitro* gene mutation assay using Chinese hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m² basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

13.2 Animal Toxicology and/or Pharmacology

In acute and repeat-dose neurotoxicity studies in female rats, oral administration of memantine and donepezil in combination resulted in increased incidence, severity, and distribution of neurodegeneration compared with memantine alone. The no-effect levels of the combination were associated with clinically relevant plasma memantine and donepezil exposures.

The relevance of these findings to humans is unknown.

14 CLINICAL STUDIES

The effectiveness of memantine hydrochloride as a treatment for patients with moderate to severe Alzheimer's disease was demonstrated in 2 randomized, double-blind, placebo-controlled clinical studies (Studies 1 and 2) conducted in the United States that assessed both cognitive function and day to day function. The mean age of patients participating in these two trials was 76 with a range of 50 -93 years. Approximately 66% of patients were female and 91% of patients were Caucasian. A third study (Study 3), carried out in Latvia, enrolled patients with severe dementia, but did not assess cognitive function as a planned endpoint. Study Outcome Measures: In each U.S. study, the effectiveness of memantine hydrochloride was determined using both an instrument designed to evaluate overall function through caregiver-related assessment, and an instrument that measures cognition. Both studies showed that patients on memantine hydrochloride experienced significant improvement on both measures compared to placebo.

Day-to-day function was assessed in both studies using the modified Alzheimer's disease Cooperative Study - Activities of Daily Living inventory (ADCS-ADL). The ADCS-ADL consists of a comprehensive battery of ADL questions used to measure the functional capabilities of patients. Each ADL item is rated from the highest level of independent performance to complete loss. The investigator

performs the inventory by interviewing a caregiver familiar with the behavior of the patient. A subset of 19 items, including ratings of the patient's ability to eat, dress, bathe, telephone, travel, shop, and perform other household chores has been validated for the assessment of patients with moderate to severe dementia. This is the modified ADCS-ADL, which has a scoring range of 0 to 54, with the lower scores indicating greater functional impairment.

The ability of Memantine Hydrochloride Tablet to improve cognitive performance was assessed in both studies with the Severe Impairment Battery (SIB), a multi-item instrument that has been validated for the evaluation of cognitive function in patients with moderate to severe dementia. The SIB examines selected aspects of cognitive performance, including elements of attention, orientation, language, memory, visuospatial ability, construction, praxis, and social interaction. The SIB scoring range is from 0 to 100, with lower scores indicating greater cognitive impairment.

Study 1 (Twenty-Eight-Week Study)

In a study of 28 weeks duration, 252 patients with moderate to severe probable Alzheimer's disease (diagnosed by DSM-IV and NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥ 3 and ≤ 14 and Global Deterioration Scale Stages 5-6) were randomized to Memantine Hydrochloride Tablet or placebo. For patients randomized to Memantine Hydrochloride Tablet, treatment was initiated at 5 mg once daily and increased weekly by 5 mg/day in divided doses to a dose of 20 mg/day (10 mg twice a day).

Effects on the ADCS-ADL

Figure 1 shows the time course for the change from baseline in the ADCS-ADL score for patients in the two treatment groups completing the 28 weeks of the study. At 28 weeks of treatment, the mean difference in the ADCS-ADL change scores for the memantine hydrochloride-treated patients compared to the patients on placebo was 3.4 units. Using an analysis based on all patients and carrying their last study observation forward (LOCF analysis), memantine hydrochloride treatment was statistically significantly superior to placebo.

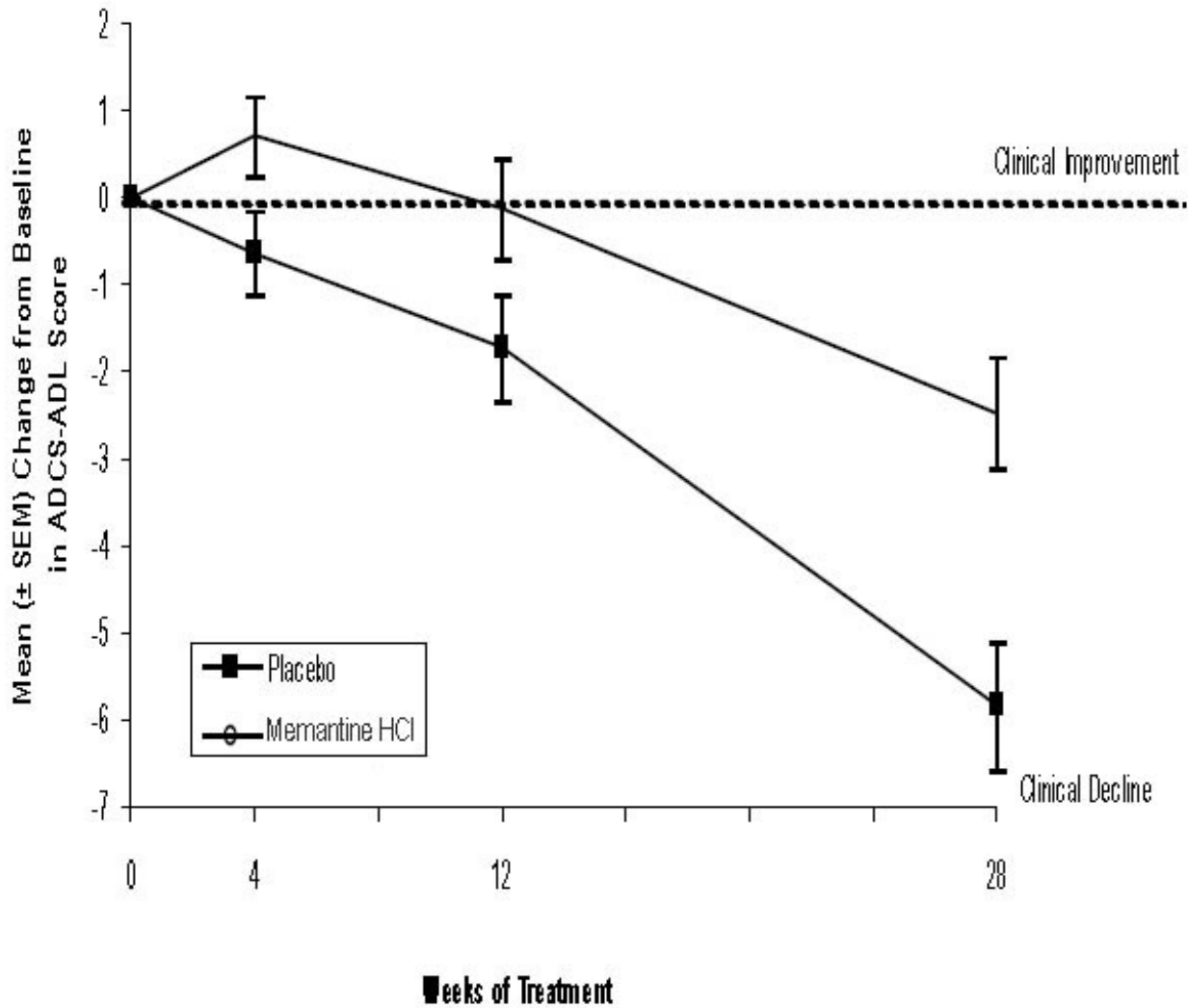


Figure 1: Time course of the change from baseline in ADCS-ADL score for patients completing 28 weeks of treatment.

Figure 2 shows the cumulative percentages of patients from each of the treatment groups who had attained at least the change in the ADCS-ADL shown on the X axis. The curves show that both patients assigned to memantine hydrochloride and placebo have a wide range of responses and generally show deterioration (a negative change in ADCS-ADL compared to baseline), but that the memantine hydrochloride group is more likely to show a smaller decline or an improvement. (In a cumulative distribution display, a curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon or shifted to the right of the curve for placebo).

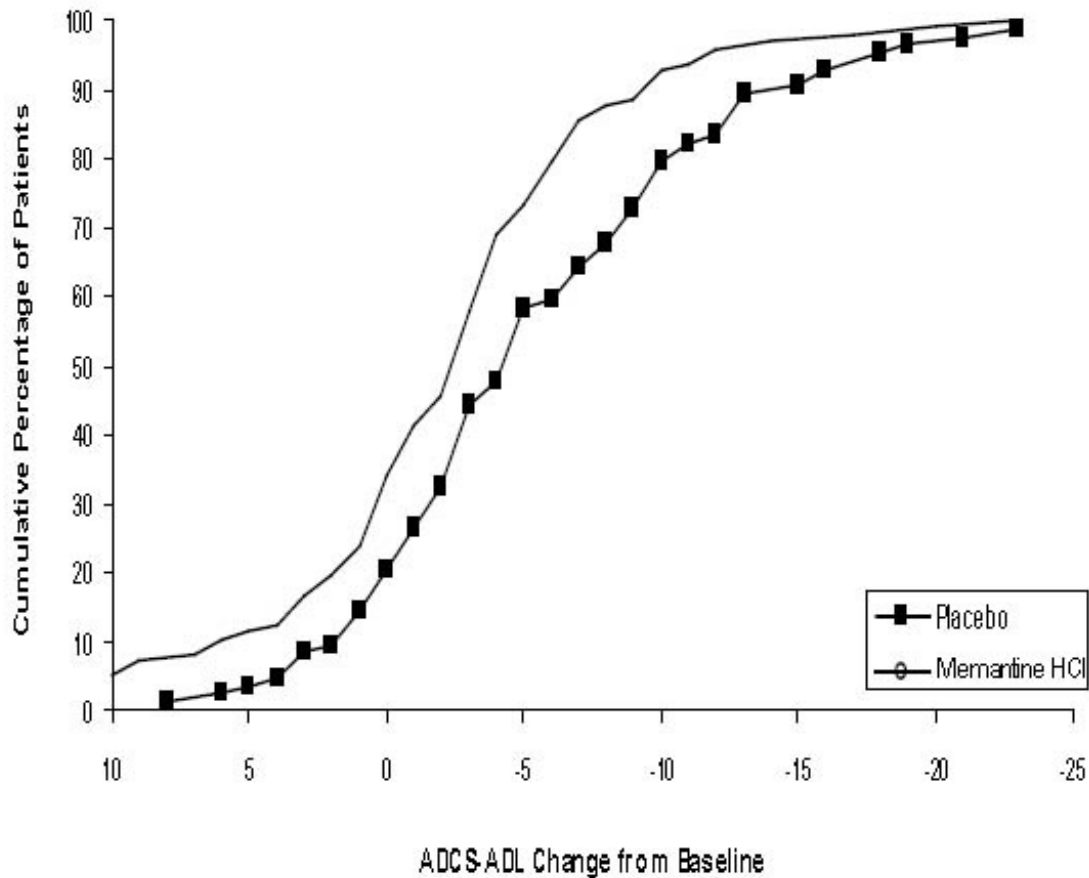


Figure 2: Cumulative percentage of patients completing 28 weeks of double-blind treatment with specified changes from baseline in ADCS-ADL scores.

Effects on the SIB

Figure 3 shows the time course for the change from baseline in SIB score for the two treatment groups over the 28 weeks of the study. At 28 weeks of treatment, the mean difference in the SIB change scores for the memantine hydrochloride-treated patients compared to the patients on placebo was 5.7 units. Using an LOCF analysis, memantine hydrochloride treatment was statistically significantly superior to placebo.

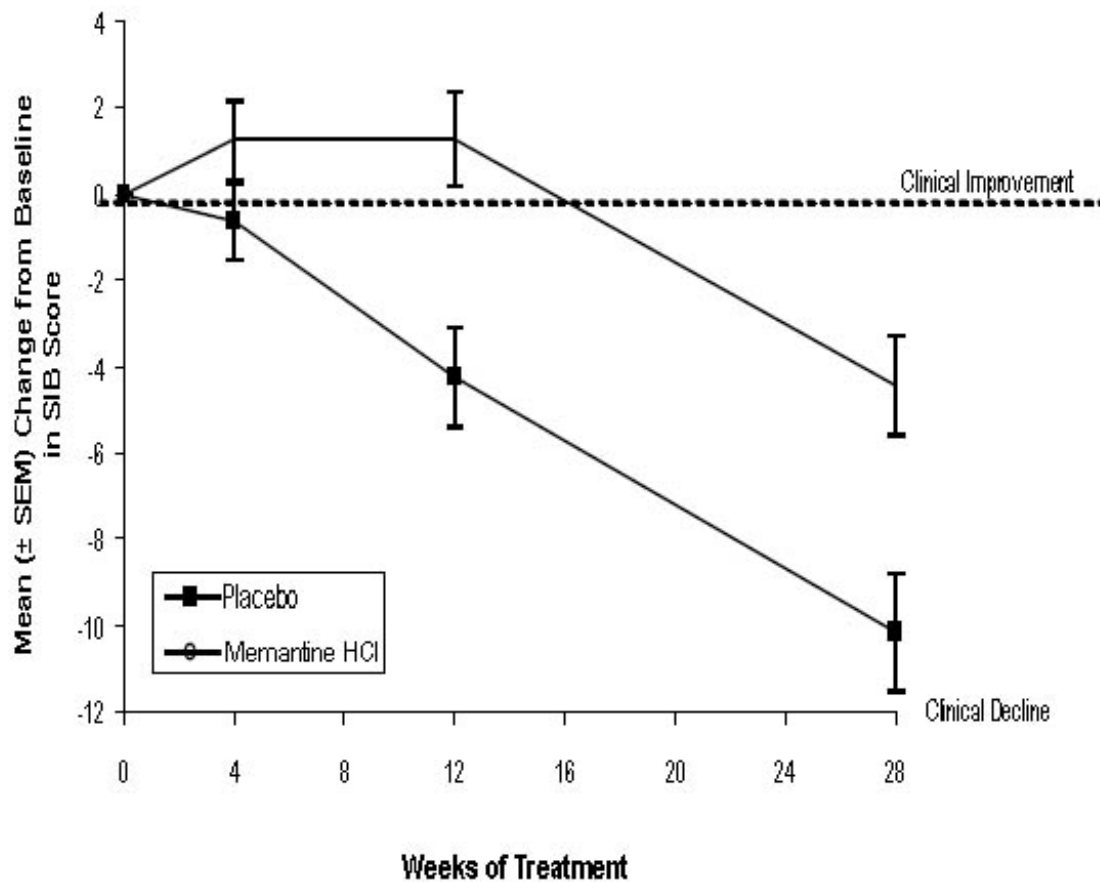


Figure 3: Time course of the change from baseline in SIB score for patients completing 28 weeks of treatment.

Figure 4 shows the cumulative percentages of patients from each treatment group who had attained at least the measure of change in SIB score shown on the X axis. The curves show that both patients assigned to memantine hydrochloride and placebo have a wide range of responses and generally show deterioration, but that the memantine hydrochloride group is more likely to show a smaller decline or an improvement.

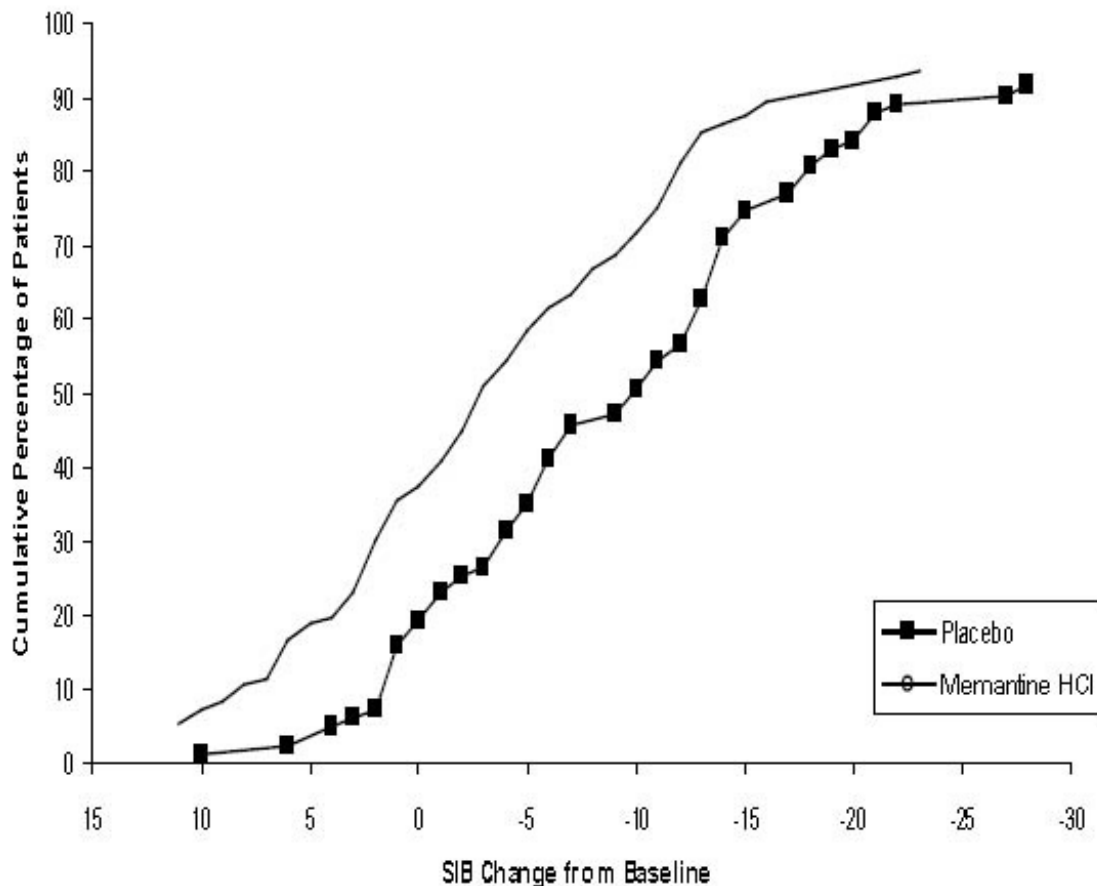


Figure 4: Cumulative percentage of patients completing 28 weeks of double-blind treatment with specified changes from baseline in SIB scores.

Study 2 (Twenty-Four-Week Study)

In a study of 24 weeks duration, 404 patients with moderate to severe probable Alzheimer's disease (diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥ 5 and ≤ 14) who had been treated with donepezil for at least 6 months and who had been on a stable dose of donepezil for the last 3 months were randomized to memantine hydrochloride or placebo while still receiving donepezil. For patients randomized to memantine hydrochloride, treatment was initiated at 5 mg once daily and increased weekly by 5 mg/day in divided doses to a dose of 20 mg/day (10 mg twice a day).

Effects on the ADCS-ADL

Figure 5 shows the time course for the change from baseline in the ADCS-ADL score for the two treatment groups over the 24 weeks of the study. At 24 weeks of treatment, the mean difference in the ADCS-ADL change scores for the memantine hydrochloride /donepezil treated patients (combination therapy) compared to the patients on placebo/donepezil (monotherapy) was 1.6 units. Using an LOCF analysis, Memantine hydrochloride /donepezil treatment was statistically significantly superior to placebo/donepezil.

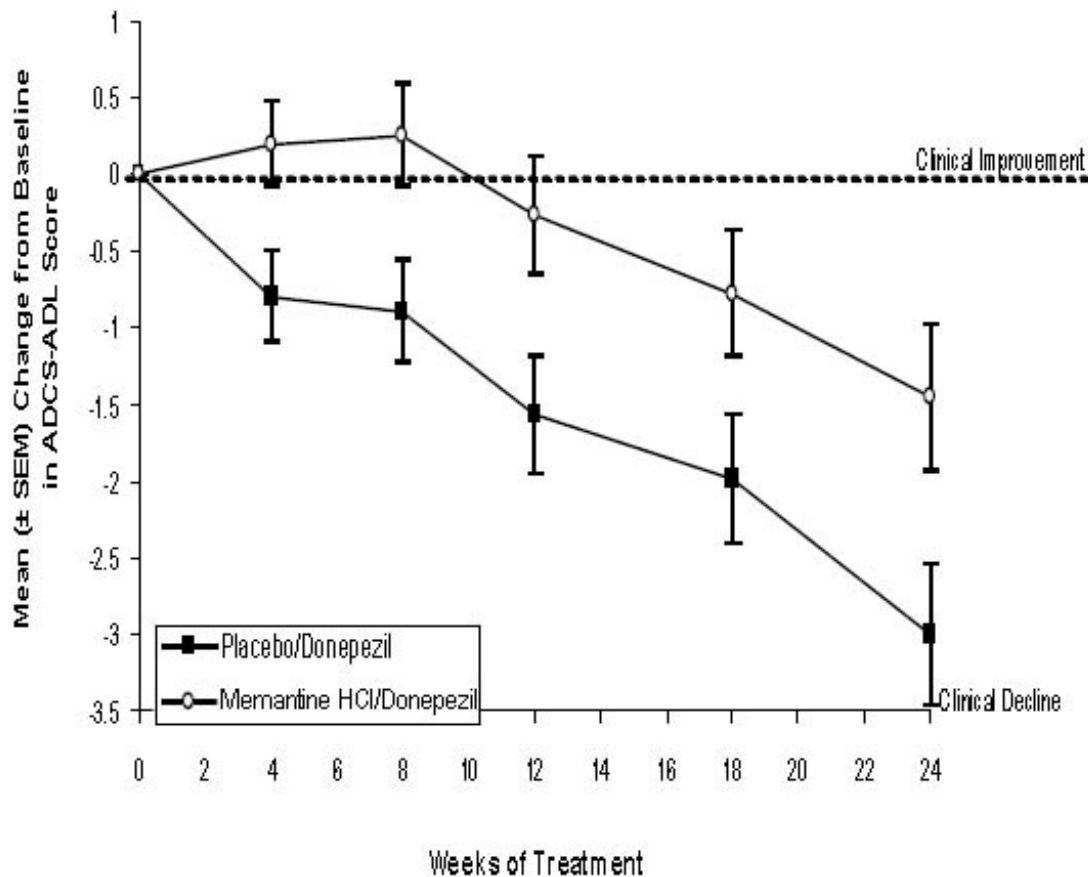


Figure 5: Time course of the change from baseline in ADCS-ADL score for patients completing 24 weeks of treatment.

Figure 6 shows the cumulative percentages of patients from each of the treatment groups who had attained at least the measure of improvement in the ADCS-ADL shown on the X axis. The curves show that both patients assigned to memantine hydrochloride/donepezil and placebo/donepezil have a wide range of responses and generally show deterioration, but that the Memantine hydrochloride/donepezil group is more likely to show a smaller decline or an improvement.

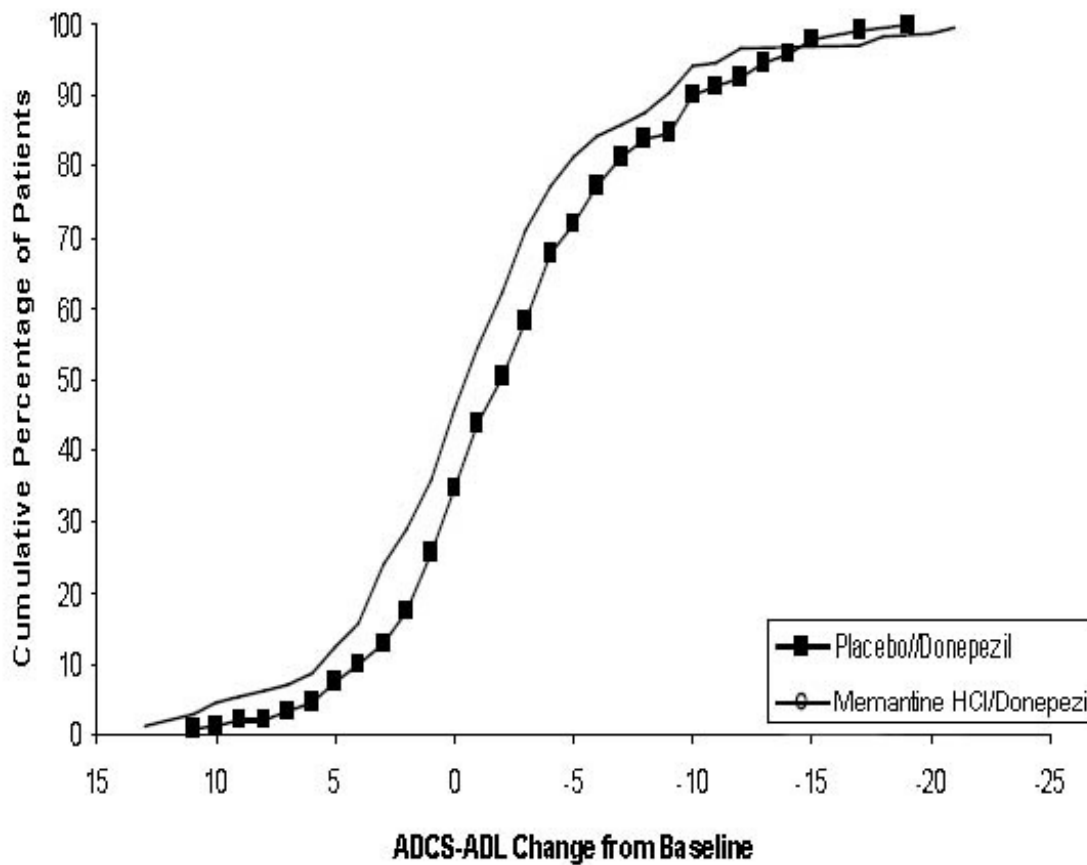


Figure 6: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in ADCS-ADL scores.

Effects on the SIB

Figure 7 shows the time course for the change from baseline in SIB score for the two treatment groups over the 24 weeks of the study. At 24 weeks of treatment, the mean difference in the SIB change scores for the memantine hydrochloride/donepezil-treated patients compared to the patients on placebo/donepezil was 3.3 units. Using an LOCF analysis, memantine hydrochloride/donepezil treatment was statistically significantly superior to placebo/donepezil.

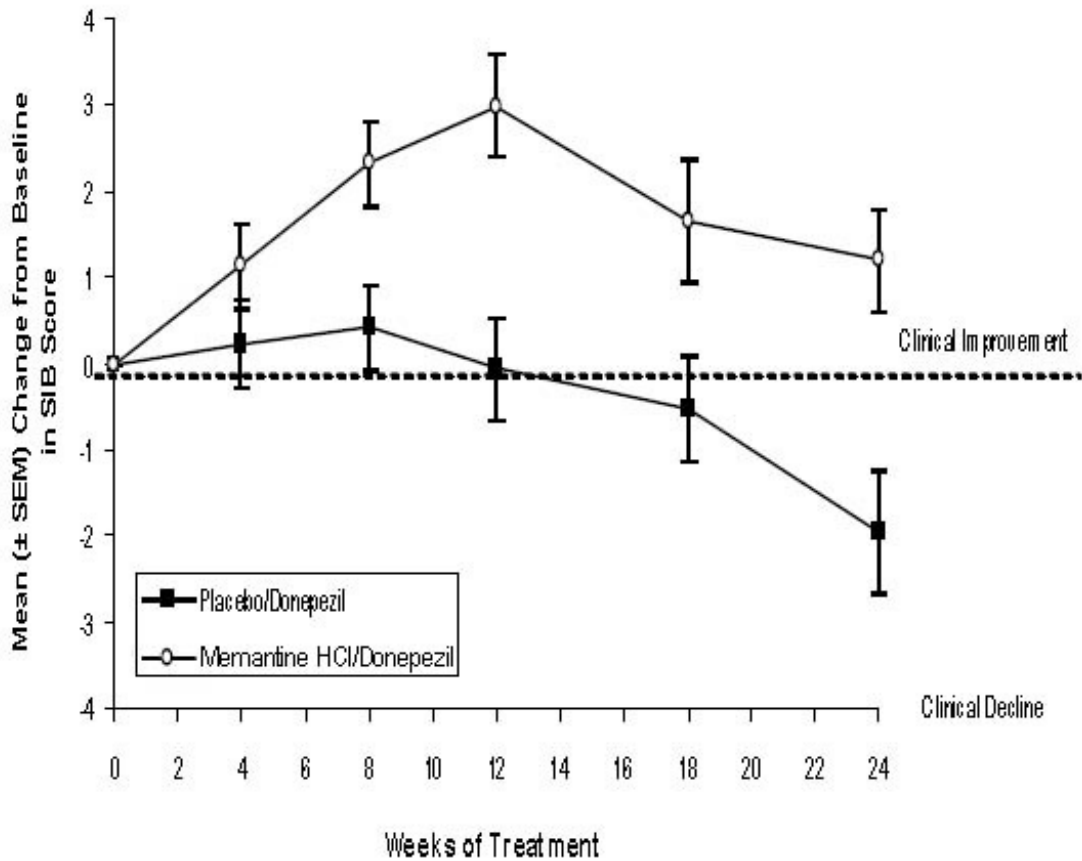


Figure 7: Time course of the change from baseline in SIB score for patients completing 24 weeks of treatment.

Figure 8 shows the cumulative percentages of patients from each treatment group who had attained at least the measure of improvement in SIB score shown on the X axis. The curves show that both patients assigned to memantine hydrochloride/donepezil and placebo/donepezil have a wide range of responses, but that the memantine hydrochloride/donepezil group is more likely to show an improvement or a smaller decline.

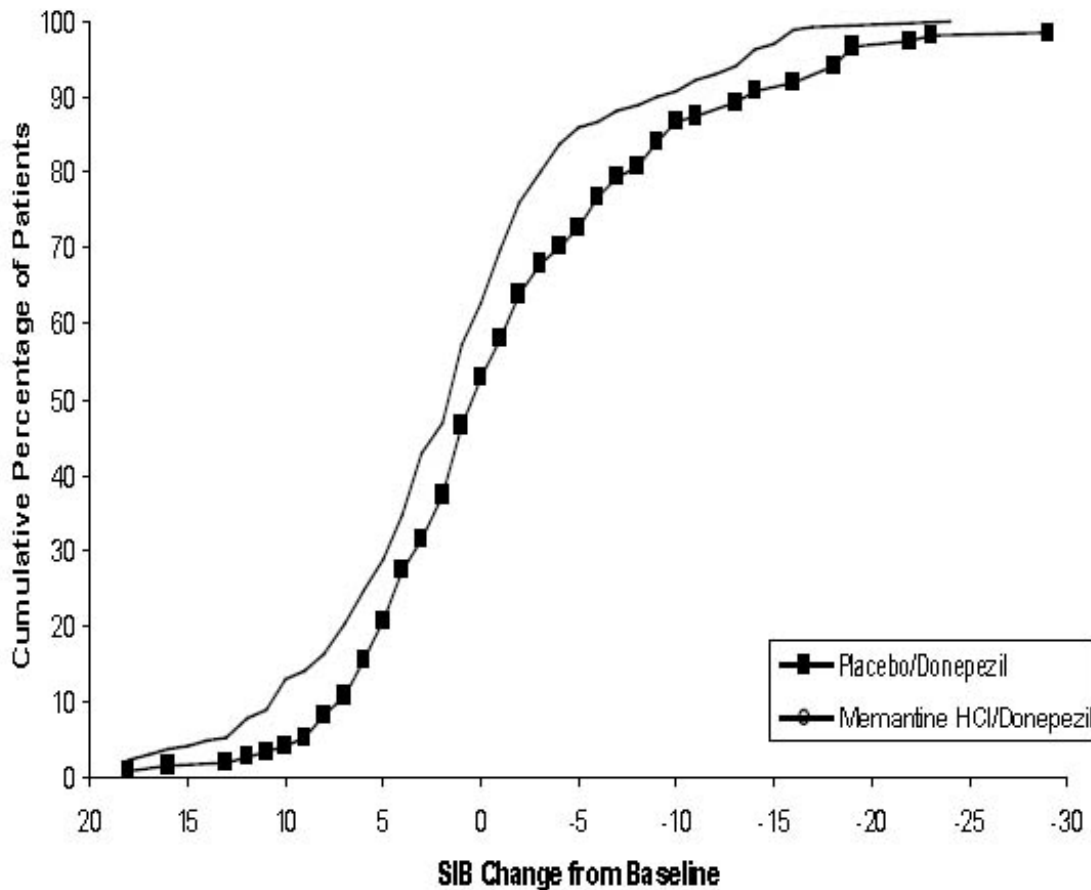


Figure 8: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in SIB scores.

Study 3 (Twelve-Week Study)

In a double-blind study of 12 weeks duration, conducted in nursing homes in Latvia, 166 patients with dementia according to DSM-III-R, a Mini-Mental State Examination score of < 10, and Global Deterioration Scale staging of 5 to 7 were randomized to either memantine hydrochloride or placebo. For patients randomized to memantine hydrochloride, treatment was initiated at 5 mg once daily and increased to 10 mg once daily after 1 week. The primary efficacy measures were the care dependency subscale of the Behavioral Rating Scale for Geriatric Patients (BGP), a measure of day-to-day function, and a Clinical Global Impression of Change (CGI-C), a measure of overall clinical effect. No valid measure of cognitive function was used in this study. A statistically significant treatment difference at 12 weeks that favored memantine hydrochloride over placebo was seen on both primary efficacy measures. Because the patients entered were a mixture of Alzheimer's disease and vascular dementia, an attempt was made to distinguish the two groups and all patients were later designated as having either vascular dementia or Alzheimer's disease, based on their scores on the Hachinski Ischemic Scale at study entry. Only about 50% of the patients had computerized tomography of the brain. For the subset designated as having Alzheimer's disease, a statistically significant treatment effect favoring memantine hydrochloride over placebo at 12 weeks was seen on both the BGP and CGI-C.

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

To assure safe and effective use of Memantine Hydrochloride Tablet, the following information and instructions provided in the patient information section should be discussed with patients and caregivers.

Patients/caregivers should be instructed to follow the dose titration schedule provided by their physician or healthcare professional for Memantine Hydrochloride Tablet. They should be warned not to use any tablets of memantine hydrochloride that are damaged or show signs of tampering.

If a patient misses a single dose of memantine hydrochloride, that patient should not double up on the next dose. The next dose should be taken as scheduled. If a patient fails to take Memantine Hydrochloride Tablet for several days, dosing should not be resumed without consulting that patient's healthcare professional.

Patient Information

Memantine Hydrochloride Tablets

Read this Patient Information that comes with Memantine Hydrochloride Tablet before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is Memantine Hydrochloride Tablet?

Memantine Hydrochloride Tablet is a prescription medicine used for the treatment of moderate to severe dementia in people with Alzheimer's disease. Memantine Hydrochloride belongs to a class of medicines called NMDA (N-methyl-D-aspartate) inhibitors.

It is not known if Memantine Hydrochloride Tablet is safe and effective in children.

Who should not take Memantine Hydrochloride Tablet?

Do not take Memantine Hydrochloride Tablet if you are allergic to memantine or any of the ingredients in Memantine Hydrochloride Tablet. See the end of this leaflet for a complete list of ingredients in Memantine Hydrochloride Tablet.

What should I tell my doctor before taking Memantine Hydrochloride Tablet?

Before you take Memantine Hydrochloride Tablet, tell your doctor if you:

- have or have had seizures
- have or have had problems passing urine
- have or have had bladder or kidney problems
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if Memantine Hydrochloride Tablet will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if memantine passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take Memantine Hydrochloride Tablet.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Taking Memantine Hydrochloride Tablet with certain other medicines may affect each other. Taking Memantine Hydrochloride Tablet with other medicines can cause serious side effects.

Especially tell your doctor if you take:

- other NMDA antagonists such as amantadine, ketamine, and dextromethorphan
- medicines that make your urine alkaline such as carbonic anhydrase inhibitors and sodium bicarbonate

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Memantine Hydrochloride Tablet?

- Your doctor will tell you how much Memantine Hydrochloride Tablet to take and when to take it.
- Your doctor may change your dose if needed.
- Memantine Hydrochloride Tablet can be taken with food or without food.
- Do not use any tablets of Memantine Hydrochloride that are damaged or show signs of tampering.
- If you forget to take one dose of Memantine Hydrochloride Tablet, do not double up on the next dose. You should take only the next dose as scheduled.
- If you have forgotten to take Memantine Hydrochloride Tablet for several days, you should not take the next dose until you talk to your doctor.
- If you take too much Memantine Hydrochloride Tablet, call your doctor or poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.

What are the possible side effects of Memantine Hydrochloride Tablet?

Memantine Hydrochloride Tablet may cause side effects, including:

The most common side effects of Memantine Hydrochloride Tablet include:

- dizziness
- headache
- confusion
- constipation

These are not all the possible side effects of Memantine Hydrochloride Tablet. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Memantine hydrochloride Tablet?

Store Memantine Hydrochloride Tablet at room temperature between 59°F to 77°F (15°C to 30°C).

What are the ingredients in Memantine Hydrochloride Tablet?

Memantine Hydrochloride tablets: Active ingredient: memantine hydrochloride

Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate

Inactive ingredients of tablet film coating: hypromellose, titanium dioxide, polyethylene glycol 400, and Triacetin

Keep Memantine Hydrochloride Tablet and all medicines out of the reach of children. General information about the safe and effective use of Memantine Hydrochloride Tablet.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not take Memantine Hydrochloride Tablet for a condition for which it was not prescribed. Do not give Memantine Hydrochloride Tablet to other people, even if they have the same condition. It may

harm them.

This Patient Information leaflet summarizes the most important information about Memantine Hydrochloride Tablet. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Memantine Hydrochloride Tablet that was written for healthcare professionals.

For more information about Memantine Hydrochloride Tablet, call Ningbo Shuangcheng Pharmaceutical Co.,Ltd at 0086-574-6398-2000.

This Patient Information has been approved by the U.S. Food and Drug Administration.

866 BinHai Fourth Road, Hangzhou Bay New Zone, Cixi city, Ningbo city, Zhejiang Province, 315336, China

DRUG: Memantine Hydrochloride

GENERIC: Memantine Hydrochloride

DOSAGE: Tablet

ADMINISTRATION: Oral

NDC: 72994-001-11

STRENGTH: 5 mg




COLOR: White

SHAPE: Round shaped film-coated

SCORE: no score

IMPRINT: M5; V

QTY: 60 Tablets

LOT No. : EXP DATE:		NDC 72994-001-11	60 Tablets	<p>Each tablet contains: 5 mg of memantine hydrochloride USP. Keep this and all drugs out of the reach of children. Dispense in a tightly closed container as described in the USP.</p> <p>Store at 25°C (77°F); Excursions permitted to 15-30°C (59°-86°F) [see USP Controlled Room Temperature]</p> <p>See package insert for dosing and full prescribing information.</p>	Manufactured by
		Memantine Hydrochloride Tablets, USP 5 mg Rx only			
					Manufactured for
					<p>Ningbo Shouzheng Medicinal Research Co., Ltd 866 BinHai Fourth Road, Hangzhou Bay New Zone, Cixi city, Ningbo city, Zhejiang Province, China</p>

DRUG: Memantine Hydrochloride

GENERIC: Memantine Hydrochloride

DOSAGE: Tablet

ADMINISTRATION: Oral

NDC: 72994-002-11

STRENGTH: 10 mg

COLOR: White

SHAPE: Round shaped film-coated

SCORE: no score

IMPRINT: M10; X

QTY: 60 Tablets

LOT No. :
EXP DATE:



NDC 72994-02-11

60 Tablets

Memantine Hydrochloride

Tablets, USP
10 mg Rx only



Each tablet contains: 10 mg of memantine hydrochloride USP.

Keep this and all drugs out of the reach of children.

Dispense in a tightly closed container as described in the USP.

Store at 25°C (77°F); Excursions permitted to 15-30°C (59°-86°F) [see USP Controlled Room Temperature]

See package insert for dosing and full prescribing information.

Manufactured by

Ningbo Shuangcheng Pharmaceuticals Co., Ltd
866 BinHai Fourth Road, Hangzhou Bay New Zone, Cixi city, Ningbo city, Zhejiang Province, China

Manufactured for

Ningbo Shouzheng Medicinal Research Co., Ltd
866 BinHai Fourth Road, Hangzhou Bay New Zone, Cixi city, Ningbo city, Zhejiang Province, China

GENERIC DRUG

memantine hydrochloride tablets tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:72994-001
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MEMANTINE HYDROCHLORIDE (UNII: JY0WD0UA60) (MEMANTINE - UNII:W8O17SJF3T)	MEMANTINE HYDROCHLORIDE	5 mg

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TRACETIN (UNII: XHX3C3X673)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
HYPROMELLOSE 2910 (6 MPAS) (UNII: 0WZ8WG20P6)	
POLYETHYLENE GLYCOL 3350 (UNII: G2M7P15E5P)	

Product Characteristics

Color	white	Score	no score
Shape	ROUND	Size	6mm
Flavor		Imprint Code	M5;V
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72994-001-11	60 in 1 BOTTLE, PLASTIC; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)	04/06/2020	04/17/2030

LOT No.:
EXP DATE:



NDC 72994-001-11

60 Tablets

Memantine Hydrochloride

Tablets, USP

5mg Rx only



Each tablet contains: 5mg of memantine hydrochloride USP.

Keep this and all drugs out of the reach of children.

Dispense in a tightly closed container as described in the USP.

Store at 25°C (77°F); Excursions permitted to 15-30°C (59°-86°F) [see USP Controlled Room Temperature]

See package insert for dosing and full prescribing information.

Manufactured by

Ningbo Shuangcheng Pharmaceutical Co., Ltd
No. 866 BinHai Fourth Road, Hangzhou Bay New Zone, Cixi city, Ningbo city, Zhejiang Province, China

Manufactured for

Ningbo Shouzheng Medicinal Research Co., Ltd
No. 866 BinHai Fourth Road, Hangzhou Bay New Zone, Cixi city, Ningbo city, Zhejiang Province, China

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		04/06/2020	04/17/2030

GENERIC DRUG

memantine hydrochloride tablets tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:72994-002
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MEMANTINE HYDROCHLORIDE (UNII: JY0WD0UA60) (MEMANTINE - UNII:W8O17SJF3T)	MEMANTINE HYDROCHLORIDE	10 mg

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TRIACETIN (UNII: XHX3C3X673)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
HYPROMELLOSE 2910 (6 MPAS) (UNII: 0WZ8WG20P6)	
POLYETHYLENE GLYCOL 3350 (UNII: G2M7P15E5P)	

Product Characteristics

Color	white	Score	no score
Shape	ROUND	Size	8mm
Flavor		Imprint Code	M10;X
Contains			

Packaging

Marketing	Marketing
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#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72994-002-11	60 in 1 BOTTLE, PLASTIC; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)	04/06/2020	04/17/2030

LOT No. :
EXP DATE:

NDC 72994-002-11 60 Tablets

Each tablet contains: 10mg of memantine hydrochloride USP.
Keep this and all drugs out of the reach of children.
Dispense in a tightly closed container as described in the USP.

Manufactured by
Ningbo Shuangcheng Pharmaceutical Co., Ltd
No. 866 BinHai Fourth Road, Hangzhou Bay New Zone, Cixi city, Ningbo city, Zhejiang Province, China

Manufactured for
Ningbo Shouzheng Medicinal Research Co., Ltd
No. 866 BinHai Fourth Road, Hangzhou Bay New Zone, Cixi city, Ningbo city, Zhejiang Province, China

Memantine Hydrochloride
Tablets, USP
10mg Rx only

See package insert for dosing and full prescribing information.

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		04/06/2020	04/17/2030

Labeler - Ningbo Shouzheng Medicinal Research Co., Ltd (544579913)

Registrant - Ningbo Shuangchenemed Pharmaceutical Co., Ltd (544337902)

Revised: 5/2019

Ningbo Shouzheng Medicinal Research Co., Ltd