

MEMANTINE AND DONEPEZIL HYDROCHLORIDES- memantine and donepezil hydrochlorides capsule, extended release

ANI Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MEMANTINE AND DONEPEZIL HYDROCHLORIDES EXTENDED-RELEASE CAPSULES safely and effectively. See full prescribing information for MEMANTINE AND DONEPEZIL HYDROCHLORIDES EXTENDED-RELEASE CAPSULES.

MEMANTINE AND DONEPEZIL HYDROCHLORIDES extended-release capsules, for oral use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

Memantine and donepezil hydrochlorides extended-release capsules are a combination of memantine hydrochloride, an NMDA receptor antagonist, and donepezil hydrochloride, an acetylcholinesterase inhibitor, indicated for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on 10 mg of donepezil hydrochloride once daily. (1)

DOSAGE AND ADMINISTRATION

- For patients on donepezil hydrochloride 10 mg only, the recommended starting dose of memantine and donepezil hydrochlorides extended-release capsules is 7 mg/10 mg, taken once daily in the evening. The dose should be increased in 7 mg increments to the recommended maintenance dose of 28 mg/10 mg. The minimum recommended interval between dose increases is one week. (2.1)
- Patients on memantine hydrochloride (10 mg twice daily or 28 mg extended-release once daily) and donepezil hydrochloride 10 mg once daily can be switched to memantine and donepezil hydrochlorides extended-release capsules 28 mg/10 mg, taken once daily in the evening. (2.1)
- Memantine and donepezil hydrochlorides extended-release capsules can be taken with or without food, whole or sprinkled on applesauce; do not divide, chew, or crush. (2.2)
- Severe renal impairment: the recommended maintenance dose for memantine and donepezil hydrochlorides extended-release capsules is 14 mg/10 mg once daily in the evening. (2.3)

DOSAGE FORMS AND STRENGTHS

Memantine and donepezil hydrochlorides extended-release capsules:

- 21 mg memantine hydrochloride and 10 mg donepezil hydrochloride (3)

CONTRAINDICATIONS

Memantine and donepezil hydrochlorides extended-release capsules are contraindicated in patients with known hypersensitivity to memantine hydrochloride, donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation. (4)

WARNINGS AND PRECAUTIONS

- Memantine and donepezil hydrochlorides extended-release capsules are likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. (5.1)
- Memantine and donepezil hydrochlorides extended-release capsules may have vagotonic effects on the sinoatrial and atrioventricular nodes manifesting as bradycardia or heart block. (5.2)
- Monitor patients for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers. (5.3)
- Memantine and donepezil hydrochlorides extended-release capsules can cause diarrhea, nausea, and vomiting. (5.4)
- Memantine and donepezil hydrochlorides extended-release capsules may cause bladder outflow obstructions. (5.5)
- Conditions that raise urine pH may decrease the urinary elimination of memantine, resulting in increased plasma levels of memantine. (5.5, 7.1)

ADVERSE REACTIONS

- The most common adverse reactions occurring at a frequency of at least 5% and greater than placebo with memantine hydrochloride extended-release 28 mg/day were headache, diarrhea, and

dizziness. (6.1)

- The most common adverse reactions occurring at a frequency of at least 5% in patients receiving donepezil hydrochloride and at twice or more the placebo rate, include diarrhea, anorexia, vomiting, nausea, and ecchymosis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ANI Pharmaceuticals, Inc. at 1-855-204-1431 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

- Combined use with NMDA antagonists: use with caution. (7.2)
- Memantine and donepezil hydrochlorides extended-release capsules may interfere with anticholinergic medications. (7.4)
- Concomitant administration of succinylcholine, similar neuromuscular blocking agents, or cholinergic agonists may lead to synergistic effect. (7.5)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Memantine and donepezil hydrochlorides extended-release capsules are indicated for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on 10 mg of donepezil hydrochloride once daily.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of memantine and donepezil hydrochlorides extended-release capsules is 28 mg/10 mg once daily.

For patients stabilized on donepezil and not currently on memantine:

For patients stabilized on donepezil hydrochloride 10 mg and not currently on memantine hydrochloride, the recommended starting dose of memantine and donepezil hydrochlorides extended-release capsules is 7 mg/10 mg, taken once a day in the evening. The dose should be increased in 7 mg increments of the memantine hydrochloride component to the recommended maintenance dose of 28 mg/10 mg once daily. The minimum recommended interval between dose increases is one week. The dose should only be increased if the previous dose has been well tolerated. The maximum dose is 28 mg/10 mg once daily.

For patients stabilized on both donepezil and memantine:

Patients stabilized on memantine hydrochloride (10 mg twice daily or 28 mg extended-release once daily) and donepezil hydrochloride 10 mg once daily can be switched to memantine and donepezil hydrochlorides extended-release capsules 28 mg/10 mg, taken once a day in the evening. Patients should start memantine and donepezil hydrochlorides extended-release capsules the day following the last dose of memantine

hydrochloride and donepezil hydrochloride administered separately.

If a patient misses a single dose of memantine and donepezil hydrochlorides extended-release capsules, the next dose should be taken as scheduled, without doubling up the dose.

2.2 Administration Information

Memantine and donepezil hydrochlorides extended-release capsules can be taken with or without food. Memantine and donepezil hydrochlorides extended-release capsules can be taken intact or may be opened, sprinkled on applesauce, and swallowed without chewing. The entire contents of each memantine and donepezil hydrochlorides extended-release capsule should be consumed; the dose should not be divided.

Except when opened and sprinkled on applesauce, as described above, memantine and donepezil hydrochlorides extended-release capsules should be swallowed whole. Memantine and donepezil hydrochlorides extended-release capsules should not be divided, chewed, or crushed.

2.3 Dosing in Patients with Severe Renal Impairment

For patients stabilized on donepezil and not currently on memantine:

For patients with severe renal impairment (creatinine clearance 5-29 mL/min, based on the Cockcroft-Gault equation) stabilized on donepezil hydrochloride 10 mg once daily and not currently on memantine hydrochloride, the recommended starting dose of memantine and donepezil hydrochlorides extended-release capsules is 7 mg/10 mg taken once a day in the evening. The dose should be increased to the recommended maintenance dose of 14 mg/10 mg once daily in the evening after a minimum of one week [see *Use in Specific Populations (8.6)*].

For patients stabilized on both donepezil and memantine:

Patients with severe renal impairment, stabilized on memantine hydrochloride (5 mg twice daily or 14 mg extended-release once daily) and donepezil hydrochloride 10 mg once daily, can be switched to memantine and donepezil hydrochlorides extended-release capsules 14 mg/10 mg, taken once daily in the evening.

3 DOSAGE FORMS AND STRENGTHS

Extended-Release Capsules:

- 21 mg memantine hydrochloride and 10 mg donepezil hydrochloride: hard gelatin capsules, with natural body and natural cap imprinted with the logo “A313” on the body and “21/10” on the cap in black ink, containing white to off-white beads

4 CONTRAINDICATIONS

Memantine and donepezil hydrochlorides extended-release capsules are contraindicated in patients with known hypersensitivity to memantine hydrochloride, donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Anesthesia

Donepezil hydrochloride, an active ingredient in memantine and donepezil hydrochlorides extended-release capsules, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

5.2 Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of donepezil hydrochloride, an active ingredient in memantine and donepezil hydrochlorides extended-release capsules.

5.3 Peptic Ulcer Disease and Gastrointestinal Bleeding

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Clinical studies of donepezil hydrochloride in a dose of 5 mg/day to 10 mg/day have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. Patients treated with memantine and donepezil hydrochlorides extended-release capsules should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs).

5.4 Nausea and Vomiting

Donepezil hydrochloride, an active ingredient in memantine and donepezil hydrochlorides extended-release capsules, when initiated, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea, and vomiting. Although in most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of donepezil hydrochloride, patients should be observed closely at the initiation of treatment.

5.5 Genitourinary Conditions

Although not observed in clinical trials of donepezil hydrochloride, an active ingredient in memantine and donepezil hydrochlorides extended-release capsules, cholinomimetics may cause bladder outflow obstruction.

Conditions that raise urine pH may decrease the urinary elimination of memantine, an active ingredient in memantine and donepezil hydrochlorides extended-release capsules, resulting in increased plasma levels of memantine [*see Drug Interactions (7.1)*].

5.6 Seizures

Cholinomimetics, including donepezil hydrochloride, an active ingredient in memantine and donepezil hydrochlorides extended-release capsules, are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a

manifestation of Alzheimer's disease.

5.7 Pulmonary Conditions

Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in the labeling.

- Cardiovascular Conditions [see *Warnings and Precautions (5.2)*]
- Peptic Ulcer Disease and Gastrointestinal Bleeding [see *Warnings and Precautions (5.3)*]
- Nausea and Vomiting [see *Warnings and Precautions (5.4)*]
- Genitourinary Conditions [see *Warnings and Precautions (5.5)*]
- Seizures [see *Warnings and Precautions (5.6)*]
- Pulmonary Conditions [see *Warnings and Precautions (5.7)*]

6.1 Clinical Trials Experience

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 practice.

Memantine Hydrochloride

Memantine hydrochloride extended-release was evaluated in a double-blind, placebo-controlled trial in 676 patients with moderate to severe dementia of the Alzheimer's type (341 patients treated with memantine 28 mg/day dose and 335 patients treated with placebo) for a treatment period up to 24 weeks. Of the patients randomized, 236 treated with memantine 28 mg/day and 227 treated with placebo were on a stable dose of donepezil for 3 months prior to screening.

Adverse Reactions Leading to Discontinuation with Memantine Hydrochloride

In the placebo-controlled clinical trial of memantine hydrochloride extended-release, the proportion of patients in the memantine hydrochloride extended-release 28 mg/day dose group and in the placebo group who discontinued treatment due to adverse reactions was 10% and 6%, respectively. The most common adverse reaction in the memantine hydrochloride extended-release treated group that led to treatment discontinuation was dizziness, at a rate of 1.5%.

Most Common Adverse Reactions with Memantine Hydrochloride

The most common adverse reactions with memantine hydrochloride extended-release in patients with moderate to severe Alzheimer's disease, defined as those occurring at a frequency of at least 5% in the memantine hydrochloride extended-release group and at a higher frequency than placebo, were headache, diarrhea, and dizziness.

Table 1 lists adverse reactions that occurred at an incidence of $\geq 2\%$ in the memantine hydrochloride extended-release treated group and occurred at a rate greater than placebo.

Table 1: Adverse reactions with memantine hydrochloride extended-release in patients with moderate to severe Alzheimer's disease

Adverse Reaction	Placebo (n=335) %	Memantine hydrochloride extended-release 28 mg (n=341) %
Gastrointestinal Disorders		
Diarrhea	4	5
Constipation	1	3
Abdominal pain	1	2
Vomiting	1	2
Infections and Infestations		
Influenza	3	4
Investigations		
Increased weight	1	3
Musculoskeletal and Connective Tissue Disorders		
Back pain	1	3
Nervous System Disorders		
Headache	5	6
Dizziness	1	5
Somnolence	1	3
Psychiatric Disorders		
Anxiety	3	4
Depression	1	3
Aggression	1	2
Renal and Urinary Disorders		
Urinary incontinence	1	2
Vascular Disorders		
Hypertension	2	4
Hypotension	1	2

Donepezil hydrochloride

Adverse Reactions Leading to Discontinuation with Donepezil Hydrochloride

In controlled clinical trials of donepezil hydrochloride, the rate of discontinuation due to adverse reactions for patients treated with donepezil hydrochloride was approximately 12%, compared to 7% for patients treated with placebo. The most common adverse reactions leading to discontinuation, defined as those occurring in at least 2% of donepezil hydrochloride patients and at twice or more the incidence seen with placebo, were anorexia (2%), nausea (2%), diarrhea (2%) and urinary tract infection (2%).

Most Common Adverse Reactions with Donepezil Hydrochloride

The most common adverse reactions reported with donepezil hydrochloride in controlled clinical trials in patients with severe Alzheimer's disease, defined as those occurring at a

frequency of at least 5% in the donepezil hydrochloride group and at twice or more the placebo rate, were diarrhea, anorexia, vomiting, nausea, and ecchymosis. The most common adverse reactions reported with donepezil hydrochloride in controlled clinical trials in patients with mild to moderate Alzheimer's disease were insomnia, muscle cramp, and fatigue.

Table 2 lists adverse reactions that occurred at an incidence of $\geq 2\%$ in the donepezil hydrochloride group and at a rate greater than placebo in controlled trials in patients with severe Alzheimer's disease.

Table 2: Adverse reactions with donepezil hydrochloride in patients with severe Alzheimer's disease

Body System/Adverse Event	Placebo (n=392) %	Donepezil hydrochloride 10 mg/day (n=501) %
Percent of Patients with any Adverse Event	73	81
Body as a Whole		
Accident	12	13
Infection	9	11
Headache	3	4
Pain	2	3
Back pain	2	3
Fever	1	2
Chest pain	<1	2
Cardiovascular System		
Hypertension	2	3
Hemorrhage	1	2
Syncope	1	2
Digestive System		
Diarrhea	4	10
Vomiting	4	8
Anorexia	4	8
Nausea	2	6
Hemic and Lymphatic System		
Ecchymosis	2	5
Metabolic and Nutritional Systems		
Increased creatine phosphokinase	1	3
Dehydration	1	2
Hyperlipemia	<1	2
Nervous System		
Insomnia	4	5
Hostility	2	3
Nervousness	2	3

Hallucinations	1	3
Somnolence	1	2
Dizziness	1	2
Depression	1	2
Confusion	1	2
Emotional lability	1	2
Personality disorder	1	2
Skin and Appendages		
Eczema	2	3
Urogenital System		
Urinary incontinence	1	2

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of memantine hydrochloride and donepezil hydrochloride. 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.

Memantine Hydrochloride

Acute renal failure, agranulocytosis, cardiac failure congestive, hepatitis, leukopenia (including neutropenia), pancreatitis, pancytopenia, Stevens Johnson Syndrome, suicidal ideation, thrombocytopenia, and thrombotic thrombocytopenic purpura.

Donepezil Hydrochloride

Abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, neuroleptic malignant syndrome, pancreatitis, and rash.

7 DRUG INTERACTIONS

7.1 Use of Memantine with 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 reactions. 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 of Memantine 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.

7.3 Effect of Other Drugs on the Metabolism of Donepezil

Inhibitors of CYP3A4 (e.g., ketoconazole) and CYP2D6 (e.g., quinidine), inhibit donepezil

metabolism *in vitro*. Whether there is a clinical effect of quinidine is not known. Inducers of CYP3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil.

7.4 Use of Donepezil with Anticholinergics

Because of their mechanism of action, cholinesterase inhibitors, including donepezil hydrochloride, have the potential to interfere with the activity of anticholinergic medications.

7.5 Use of Donepezil with Cholinomimetics and Other Cholinesterase Inhibitors

A synergistic effect may be expected when cholinesterase inhibitors, including donepezil hydrochloride, are given concurrently with succinylcholine, similar neuromuscular blocking agents, or cholinergic agonists such as bethanechol.

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 and donepezil hydrochlorides extended-release capsules or its active ingredients (memantine hydrochloride and donepezil hydrochloride) in pregnant women.

Adverse developmental effects (mortality and decreased body weight and skeletal ossification) were observed in the offspring of rats administered memantine or donepezil during pregnancy at doses associated with minimal maternal toxicity. These doses are higher than those used in humans at the recommended daily dose of memantine and donepezil hydrochlorides extended-release capsules [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

Memantine Hydrochloride

Oral administration of memantine (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 2 times the dose of memantine at the recommended human daily dose (RHD) of memantine and donepezil hydrochlorides extended-release capsules (28 mg memantine/10 mg donepezil) on a body surface area (mg/m²) basis.

Oral administration of memantine to rabbits (3, 10, or 30 mg/kg/day) during the period of organogenesis resulted in no adverse developmental effects. The highest dose tested is approximately 20 times the dose of memantine at the RHD of memantine and

donepezil hydrochlorides extended-release capsules on a mg/m² basis.

In rats, memantine (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 2 times the dose of memantine at the RHD of memantine and donepezil hydrochlorides extended-release capsules on a mg/m² basis.

Oral administration of memantine (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 2 times the dose of memantine at the RHD of memantine and donepezil hydrochlorides extended-release capsules on a mg/m² basis.

Donepezil Hydrochloride

Oral administration of donepezil to rats and rabbits during the period of organogenesis resulted in no adverse developmental effects. The highest doses (16 and 10 mg/kg/day, respectively) were approximately 15 and 7 times, respectively, the dose of donepezil at the RHD of memantine and donepezil hydrochlorides extended-release capsules on a mg/m² basis.

Oral administration of donepezil (1, 3, or 10 mg/kg/day) to rats during late gestation and throughout lactation to weaning resulted in an increase in stillbirths and offspring mortality at the highest dose tested. The higher no-effect dose (3 mg/kg/day) is approximately 3 times the dose of donepezil at the RHD of memantine and donepezil hydrochlorides extended-release capsules on a mg/m² basis.

8.2 Lactation

Risk Summary

There are no data on the presence of memantine or donepezil in human milk, the effects on the breastfed infant, or the effects of memantine and donepezil hydrochlorides extended-release capsules or its metabolites on milk production.

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

8.4 Pediatric Use

Safety and effectiveness of memantine and donepezil hydrochlorides extended-release capsules 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 Reactions (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 3:

Table 3: 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 4:

Table 4: 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%).

In a juvenile animal study, male and female juvenile rats were administered memantine (15, 30, and 45 mg/kg/day) starting on postnatal day (PND) 14 through PND 70. Body weights were reduced at 45 mg/kg/day. Delays in sexual maturation were noted in male and female rats at doses ≥ 30 mg/kg/day. Memantine induced neuronal lesions in several areas of the brain on PND 15 and 17 at doses ≥ 30 mg/kg/day. Behavioral toxicity (decrease percent of auditory startle habituation) was noted for animals in the 45 mg/kg/day dose group. The 15 mg/kg/day dose was considered the No-Observed-Adverse-Effect-Level (NOAEL) for this study.

In a second juvenile rat toxicity study, male and female juvenile rats were administered memantine (1, 3, 8, 15, 30, and 45 mg/kg/day) starting on postnatal day (PND) 7 through PND 70. Due to early memantine-related mortality, the 30 and 45 mg/kg/day dose groups were terminated without further evaluation. Memantine induced apoptosis or neuronal degeneration in several areas of the brain on PND 8, 10, and 17 at a dose of 15 mg/kg/day. The NOAEL for apoptosis and neuronal degeneration was 8 mg/kg/day. Behavioral toxicity (effects on motor activity, auditory startle habituation, and learning and memory) was noted at doses ≥ 3 mg/kg/day during treatment, but was not seen after drug discontinuation. Therefore, the 1 mg/kg/day dose was considered the NOAEL for the neurobehavioral effect in this study.

8.5 Geriatric Use

Memantine Hydrochloride

The majority of people with Alzheimer's disease are 65 years and older. In the clinical study of memantine hydrochloride extended-release, the mean age of patients was approximately 77 years; over 91% of patients were 65 years of age and older, 67% were 75 years of age and older, and 14% were 85 years of age and older. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically meaningful differences in most adverse events reported by patients ≥ 65 years old and < 65 years old.

Donepezil Hydrochloride

The mean age of patients enrolled in the clinical studies with donepezil was 73 years; 80% of these patients were between 65 and 84 years of age, and 49% of patients 75 years of age and older. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patients ≥ 65 years old and < 65 years old.

8.6 Renal Impairment

A dosage reduction is recommended in patients with severe renal impairment [see *Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*]. No dosage adjustment is needed in patients with mild or moderate renal impairment.

8.7 Hepatic Impairment

No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Memantine and donepezil hydrochlorides extended-release capsules have not been studied in patients with severe hepatic impairment [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Memantine hydrochloride and donepezil hydrochloride are the two active ingredients of memantine and donepezil hydrochlorides extended-release capsules. No specific antidote for memantine hydrochloride overdose is known; however, elimination of memantine can be increased by acidification of the urine. Tertiary anticholinergics such as atropine may be used as an antidote for donepezil hydrochloride overdose. In managing cases of overdose, consider the possibility of multiple drug involvement. In case of overdose, call Poison Control Center at 1-800-222-1222 for the latest recommendation. In general, supportive measures should be utilized, and treatment should be symptomatic.

Memantine Hydrochloride

Signs and symptoms most often accompanying overdosage with other formulations of memantine 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 grams in an individual who took memantine in conjunction with unspecified antidiabetic medications. This person experienced coma, diplopia, and agitation, but subsequently recovered.

One patient participating in a memantine hydrochloride extended-release clinical trial unintentionally took 112 mg of memantine hydrochloride extended-release daily for 31 days and experienced elevated serum uric acid, elevated serum alkaline phosphatase, and low platelet count.

No fatalities have been noted with overdoses of memantine alone. A fatal outcome has very rarely been reported when memantine has been ingested as part of overdosing with multiple drugs; in those instances, the relationship between memantine and a fatal outcome has been unclear.

Donepezil Hydrochloride

Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse, and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for donepezil hydrochloride overdosage.

Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether donepezil hydrochloride and/or its metabolites can be removed by dialysis

(hemodialysis, peritoneal dialysis, or hemofiltration).

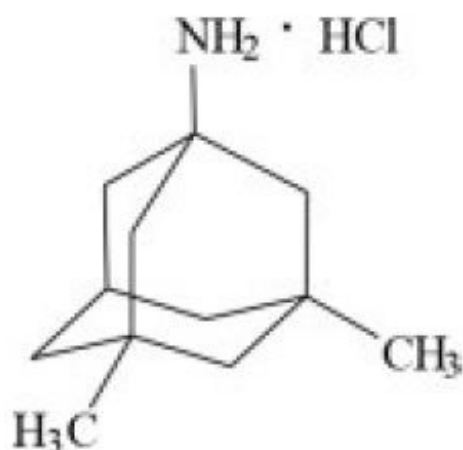
Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation, and lower body surface temperature.

11 DESCRIPTION

Memantine and donepezil hydrochlorides extended-release capsules contain memantine, an orally active NMDA receptor antagonist, as the hydrochloride salt and donepezil, a reversible inhibitor of the enzyme acetylcholinesterase, as the hydrochloride salt.

Memantine Hydrochloride

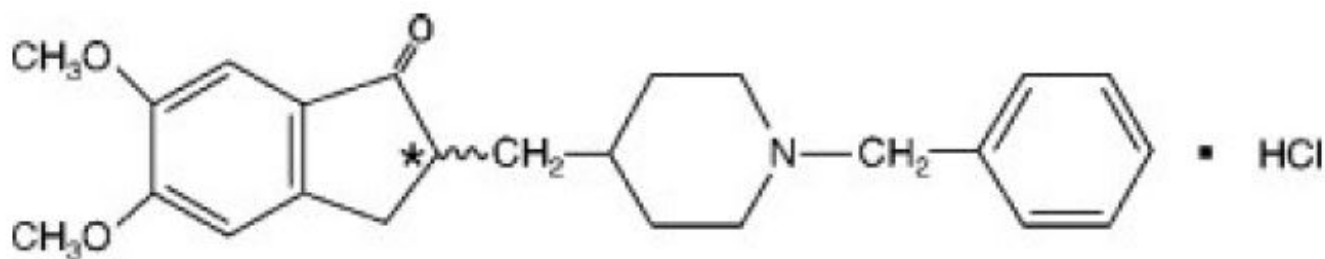
The chemical name for memantine hydrochloride is 1-amino-3,5-dimethyladamantane hydrochloride with the following structural formula:



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

Donepezil Hydrochloride

The chemical name for donepezil hydrochloride is 2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidiny]methyl]-1H-inden-1-one hydrochloride.



The molecular formula is C₂₄H₂₉NO₃●HCl and the molecular weight is 415.96. Donepezil

hydrochloride is a white crystalline powder.

Memantine and donepezil hydrochlorides extended-release capsules contain 21 mg memantine hydrochloride, 10 mg donepezil hydrochloride, and the following inactive ingredients: colloidal silicon dioxide, ethylcellulose, hydroxypropyl cellulose, hypromellose, polyethylene glycol, sugar spheres (consisting of sugar syrup, corn starch, and sucrose) and talc. The hard gelatin capsules contain black iron oxide and gelatin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Memantine and donepezil hydrochlorides extended-release capsules contain two approved medications: memantine hydrochloride and donepezil hydrochloride. Each of those medications is postulated to have a different mechanism in Alzheimer's disease.

Memantine

Persistent activation of central nervous system 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.

Donepezil

Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's disease attribute some of them to a deficiency of cholinergic neurotransmission. Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine in the central nervous system through reversible inhibition of its hydrolysis by acetylcholinesterase. There is no evidence that donepezil prevents or slows neurodegeneration in patients with Alzheimer's disease.

12.3 Pharmacokinetics

Memantine and donepezil hydrochlorides extended-release capsules

Memantine and donepezil hydrochlorides extended-release capsules were bioequivalent to co-administration of individual memantine hydrochloride extended-release and donepezil hydrochloride.

Exposure (AUC and C_{max}) of memantine and donepezil following memantine and donepezil hydrochlorides extended-release capsule administration in the fed or fasted state was similar. Further, exposure of memantine and donepezil following memantine and donepezil hydrochlorides extended-release capsule administration as intact capsule or capsule contents sprinkled on applesauce was similar in healthy subjects.

Memantine Hydrochloride

Memantine is well absorbed after oral administration and has linear pharmacokinetics

over the therapeutic dose range. It is excreted predominantly unchanged in urine and has a terminal elimination half-life of about 60-80 hours. In a study comparing 28 mg once-daily memantine hydrochloride extended-release to 10 mg twice-daily memantine hydrochloride, C_{max} and AUC_{0-24} values were 48% and 33% higher for the memantine hydrochloride extended-release dosage regimen, respectively.

Absorption

After multiple dose administration of memantine hydrochloride extended-release, memantine peak concentrations occur around 9-12 hours postdose. There is no difference in the absorption of memantine hydrochloride extended-release when the capsule is taken intact or when the contents are sprinkled on applesauce.

After single-dose administration, there is no difference in memantine exposure, based on C_{max} or AUC, for memantine hydrochloride extended-release when the drug product is administered with food or on an empty stomach. However, peak plasma concentrations are achieved about 18 hours after administration with food versus approximately 25 hours after administration on an empty stomach.

Distribution

The mean volume of distribution of memantine is 9-11 L/kg and the plasma protein binding is low (45%).

Metabolism

Memantine undergoes partial hepatic metabolism. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of memantine.

Elimination

Memantine is excreted predominantly in the urine, unchanged, and has a terminal elimination half-life of about 60-80 hours. About 48% of administered drug is excreted unchanged in urine; 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 Special Populations

Renal Impairment

Memantine pharmacokinetics were evaluated following single oral administration of 20 mg memantine hydrochloride in 8 subjects with mild renal impairment (creatinine clearance, CL_{cr} , > 50 - 80 mL/min), 8 subjects with moderate renal impairment (CL_{cr} 30 - 49 mL/min), 7 subjects with severe renal impairment (CL_{cr} 5 - 29 mL/min) and 8 healthy subjects (CL_{cr} > 80 mL/min) matched as closely as possible by age, weight and gender to the subjects with renal impairment. Mean $AUC_{0-\infty}$ increased by 4%, 60%, and 115% in subjects with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects. The terminal elimination half-life increased by 18%, 41%, and 95% in subjects with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects [see *Dosage and Administration (2.3)* and *Use in Specific Populations (8.6)*].

Hepatic Impairment

Memantine pharmacokinetics were evaluated following the administration of single oral doses of 20 mg in 8 subjects with moderate hepatic impairment (Child-Pugh Class B, score 7-9) and 8 subjects who were age-, gender-, and weight-matched to the hepatically-impaired subjects. There was no change in memantine exposure (based on C_{max} and AUC) in subjects with moderate hepatic impairment as compared with healthy subjects. However, terminal elimination half-life increased by about 16% in subjects with moderate hepatic impairment as compared with healthy subjects. The pharmacokinetics of memantine has not been evaluated in patients with severe hepatic impairment.

Gender

Following multiple dose administration of memantine hydrochloride 20 mg daily, females had about 45% higher exposure than males, but there was no difference in exposure when body weight was taken into account.

Elderly

The pharmacokinetics of memantine in young and elderly subjects are similar.

Drug-Drug Interactions

Use with Cholinesterase Inhibitors

Coadministration of memantine with the AChE inhibitor donepezil hydrochloride did not affect the pharmacokinetics of either compound. Furthermore, memantine did not affect AChE inhibition by donepezil. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine immediate-release and donepezil was similar to that of donepezil alone.

Effect of Memantine on the Metabolism of Other Drugs

In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, *in vitro* studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isozymes CYP1A2, -2C9, -2E1 and -3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Pharmacokinetic studies evaluated the potential of memantine for interaction with warfarin and bupropion. Memantine did not affect the pharmacokinetics of the CYP2B6 substrate bupropion or its metabolite hydroxybupropion. Furthermore, memantine did not affect the pharmacokinetics or pharmacodynamics of warfarin as assessed by prothrombin INR.

Effect of Other Drugs on Memantine

Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the pharmacokinetics of memantine. A single dose of bupropion did not affect the pharmacokinetics of memantine at steady state.

Drugs Eliminated via Renal Mechanisms

Because memantine is eliminated in part by tubular secretion, coadministration of drugs

that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of memantine hydrochloride and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%. In addition, coadministration of memantine hydrochloride with the antihyperglycemic drug Glucovance[®] (glyburide and metformin hydrochloride) did not affect the pharmacokinetics of memantine, metformin, and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Glucovance[®], indicating the absence of a pharmacodynamic interaction.

Drugs Highly Bound to Plasma Proteins

Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely.

Donepezil Hydrochloride

Pharmacokinetics of donepezil are linear over a dose range of 1-10 mg given once daily. The rate and extent of absorption of donepezil hydrochloride tablets are not influenced by food.

Donepezil is absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3 to 4 hours.

The elimination half-life of donepezil is about 70 hours, and the mean apparent plasma clearance (Cl/F) is 0.13 - 0.19 L/hr/kg. Following multiple dose administration, donepezil accumulates in plasma by 4-7 fold, and steady state is reached within 15 days. The steady-state volume of distribution is 12 - 16 L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly to albumins (about 75%) and alpha-1-acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/mL.

Donepezil is both excreted in the urine intact and extensively metabolized to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of ¹⁴C-labeled donepezil, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil (53%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil *in vitro* and was found in plasma at concentrations equal to about 20% of donepezil. Approximately 57% and 15% of the total radioactivity was recovered in urine and feces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug. Examination of the effect of CYP2D6 genotype in Alzheimer's patients showed differences in clearance values among CYP2D6 genotype subgroups. When compared to the extensive metabolizers, poor metabolizers had a 31.5% slower clearance and ultra-rapid metabolizers had a 24% faster clearance. These results suggest CYP2D6 has a minor role in the metabolism of donepezil.

Renal Impairment

In a study of 11 patients with moderate to severe renal impairment (CL_{cr} < 18 mL/min/1.73 m²) the clearance of donepezil hydrochloride did not differ from 11 age- and sex-matched healthy subjects.

Hepatic Disease

In a study of 10 patients with stable alcoholic cirrhosis, the clearance of donepezil hydrochloride was decreased by 20% relative to 10 healthy age- and sex-matched subjects.

Age

No formal pharmacokinetic study was conducted to examine age-related differences in the pharmacokinetics of donepezil hydrochloride. Population pharmacokinetic analysis suggested that the clearance of donepezil in patients decreases with increasing age. When compared with 65-year old subjects, 90-year old subjects have a 17% decrease in clearance, while 40-year old subjects have a 33% increase in clearance. The effect of age on donepezil clearance may not be clinically significant.

Gender and Race

No specific pharmacokinetic study was conducted to investigate the effects of gender and race on the disposition of donepezil hydrochloride. However, retrospective pharmacokinetic analysis and population pharmacokinetic analysis of plasma donepezil concentrations measured in patients with Alzheimer's disease indicate that gender and race (Japanese and Caucasians) did not affect the clearance of donepezil hydrochloride to an important degree.

Body weight

There was a relationship noted between body weight and clearance. Over the range of body weight from 50 kg to 110 kg, clearance increased from 7.77 L/h to 14.04 L/h, with a value of 10 L/h for 70 kg individuals.

Drug-Drug Interactions

Effect of Donepezil hydrochloride on the Metabolism of Other Drugs

No *in vivo* clinical trials have investigated the effect of donepezil hydrochloride on the clearance of drugs metabolized by CYP3A4 (e.g., cisapride, terfenadine) or by CYP2D6 (e.g., imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Based on *in vitro* studies, donepezil shows little or no evidence of direct inhibition of CYP2B6, CYP2C8, and CYP2C19 at clinically relevant concentrations.

Whether donepezil hydrochloride has any potential for enzyme induction is not known. Formal pharmacokinetic studies evaluated the potential of donepezil hydrochloride for interaction with theophylline, cimetidine, warfarin, digoxin, and ketoconazole. No effects of donepezil hydrochloride on the pharmacokinetics of these drugs were observed.

Effect of Other Drugs on the Metabolism of Donepezil hydrochloride

A small effect of CYP2D6 inhibitors was identified in a population pharmacokinetic analysis of plasma donepezil concentrations measured in patients with Alzheimer's disease. Donepezil clearance was reduced by approximately 17% in patients taking 10 or 23 mg in combination with a known CYP2D6 inhibitor. This result is consistent with the conclusion that CYP2D6 is a minor metabolic pathway of donepezil.

Formal pharmacokinetic studies demonstrated that the metabolism of donepezil hydrochloride is not significantly affected by concurrent administration of digoxin or

cimetidine.

An *in vitro* study showed that donepezil was not a substrate of P-glycoprotein.

Drugs Highly Bound to Plasma Proteins

Drug displacement studies have been performed *in vitro* between this highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil hydrochloride at concentrations of 0.3-10 micrograms/mL did not affect the binding of furosemide (5 micrograms/mL), digoxin (2 ng/mL), and warfarin (3 micrograms/mL) to human albumin. Similarly, the binding of donepezil hydrochloride to human albumin was not affected by furosemide, digoxin, and warfarin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Memantine

There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (7 times the dose of memantine at the maximum recommended human dose [MRHD] of memantine and donepezil hydrochlorides extended-release capsules [28 mg/10 mg] 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 (14 and 7 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 (6 times the dose of memantine at the MRHD of memantine and donepezil hydrochlorides extended-release capsules 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.

Donepezil

No evidence of carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil conducted in mice at oral doses up to 180 mg/kg/day (approximately 90 times the dose of donepezil at the MRHD of memantine and donepezil hydrochlorides extended-release capsules on a mg/m² basis), or in a 104-week carcinogenicity study in rats at oral doses up to 30 mg/kg/day (approximately 30 times the dose of donepezil at the MRHD of memantine and donepezil hydrochlorides extended-release capsules on a mg/m² basis).

Donepezil was negative in a battery of genotoxicity assays (*in vitro* bacterial reverse mutation, *in vitro* mouse lymphoma *tk*, *in vitro* chromosomal aberration, and *in vivo* mouse micronucleus).

Donepezil had no effect on fertility in rats at oral doses up to 10 mg/kg/day (approximately 10 times the dose of donepezil at the MRHD of memantine and donepezil

hydrochlorides extended-release capsules on a mg/m² basis) when administered to males and females prior to and during mating and continuing in females through implantation.

13.2 Animal Toxicology and/or Pharmacology

Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats, similar to those which are known to occur in rodents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine. In a study in which rats were given daily oral doses of memantine for 14 days, the no-effect dose for neuronal necrosis was 4 times the dose of memantine at the MRHD of memantine and donepezil hydrochlorides extended-release capsules on a mg/m² basis.

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 and donepezil hydrochlorides extended-release capsules as a treatment for patients with moderate to severe Alzheimer's disease was established by demonstrating the bioequivalence of memantine and donepezil hydrochlorides extended-release capsules with co-administered memantine hydrochloride extended-release and donepezil hydrochloride [see *Clinical Pharmacology* (12.3)].

Memantine Hydrochloride

The effectiveness of memantine hydrochloride extended-release as a treatment for patients with moderate to severe Alzheimer's disease when coadministered with acetylcholinesterase inhibitors, including donepezil hydrochloride, was based on the results of a double-blind, placebo-controlled trial.

24-week Study of Memantine Hydrochloride Extended-Release

This was a randomized, double-blind clinical investigation in 677 outpatients with moderate to severe Alzheimer's disease (diagnosed by DSM-IV criteria and NINCDS-ADRDA criteria for AD with a Mini Mental State Examination [MMSE] score ≥ 3 and ≤ 14 at Screening and Baseline) receiving acetylcholinesterase inhibitor (AChEI) therapy at a stable dose for 3 months prior to screening. Approximately 68% of the patients received donepezil as the AChEI. The mean age of patients participating in this trial was 76.5 years, with a range of 49-97 years. Approximately 72% of patients were female and 94% were Caucasian.

Study Outcome Measures

The effectiveness of memantine hydrochloride extended-release was evaluated in this study using the co-primary efficacy parameters of Severe Impairment Battery (SIB) and the Clinician's Interview-Based Impression of Change (CIBIC-Plus).

The ability of memantine hydrochloride extended-release to improve cognitive performance was assessed 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.

The ability of memantine hydrochloride extended-release to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-Plus. The CIBIC-Plus is not a single instrument and is not a standardized instrument like the ADCS-ADL or SIB. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-Plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC-Plus evaluations from other clinical trials. The CIBIC-Plus used in this trial was a structured instrument based on a comprehensive evaluation at baseline and subsequent time points of four domains: general (overall clinical status), functional (including activities of daily living), cognitive, and behavioral. It represents the assessment of a skilled clinician using validated scales based on his/her observation during an interview with the patient, in combination with information supplied by a caregiver familiar with the behavior of the patient over the interval rated. The CIBIC-Plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "marked improvement" to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening." The CIBIC-Plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

Study Results

In this study, 677 patients were randomized to one of the following 2 treatments: memantine hydrochloride extended-release 28 mg/day or placebo, while still receiving an AChEI (either donepezil, galantamine, or rivastigmine).

Effects on Severe Impairment Battery (SIB)

Figure 1 shows the time course for the change from baseline in SIB score for the two treatment groups completing the 24 weeks of the study. At 24 weeks of treatment, the mean difference in the SIB change scores for the memantine hydrochloride extended-release 28 mg/AChEI-treated (combination therapy) patients compared to the patients on placebo/AChEI (monotherapy) was 2.6 units. Using an LOCF analysis, memantine hydrochloride extended-release 28 mg/AChEI treatment was statistically significantly superior to placebo/AChEI.

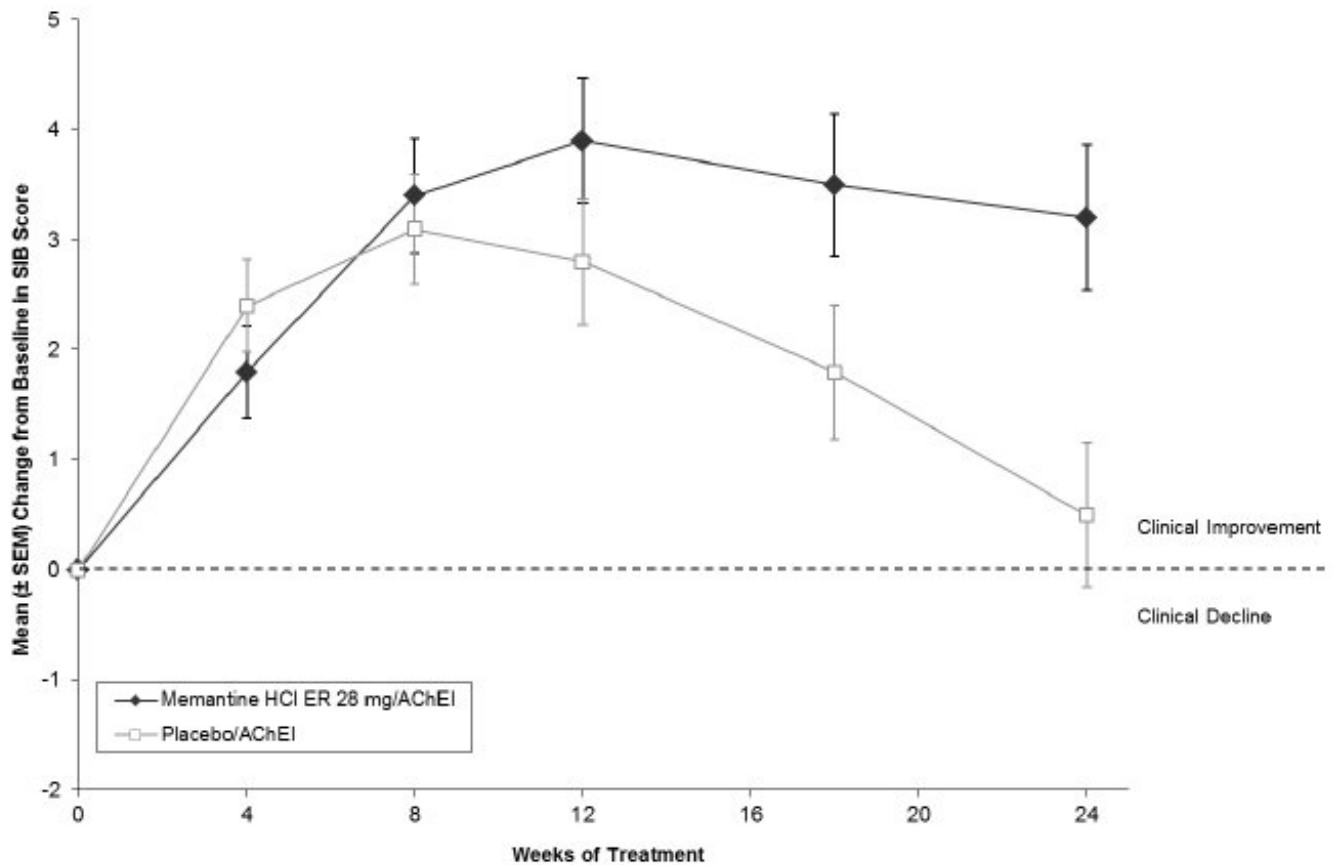


Figure 1: Time course of the change from baseline in SIB score for patients completing 24 weeks of treatment.

Figure 2 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 extended-release 28 mg/AChEI and placebo/AChEI have a wide range of responses, but that the memantine hydrochloride extended-release 28 mg/AChEI group is more likely to show an improvement or a smaller decline.

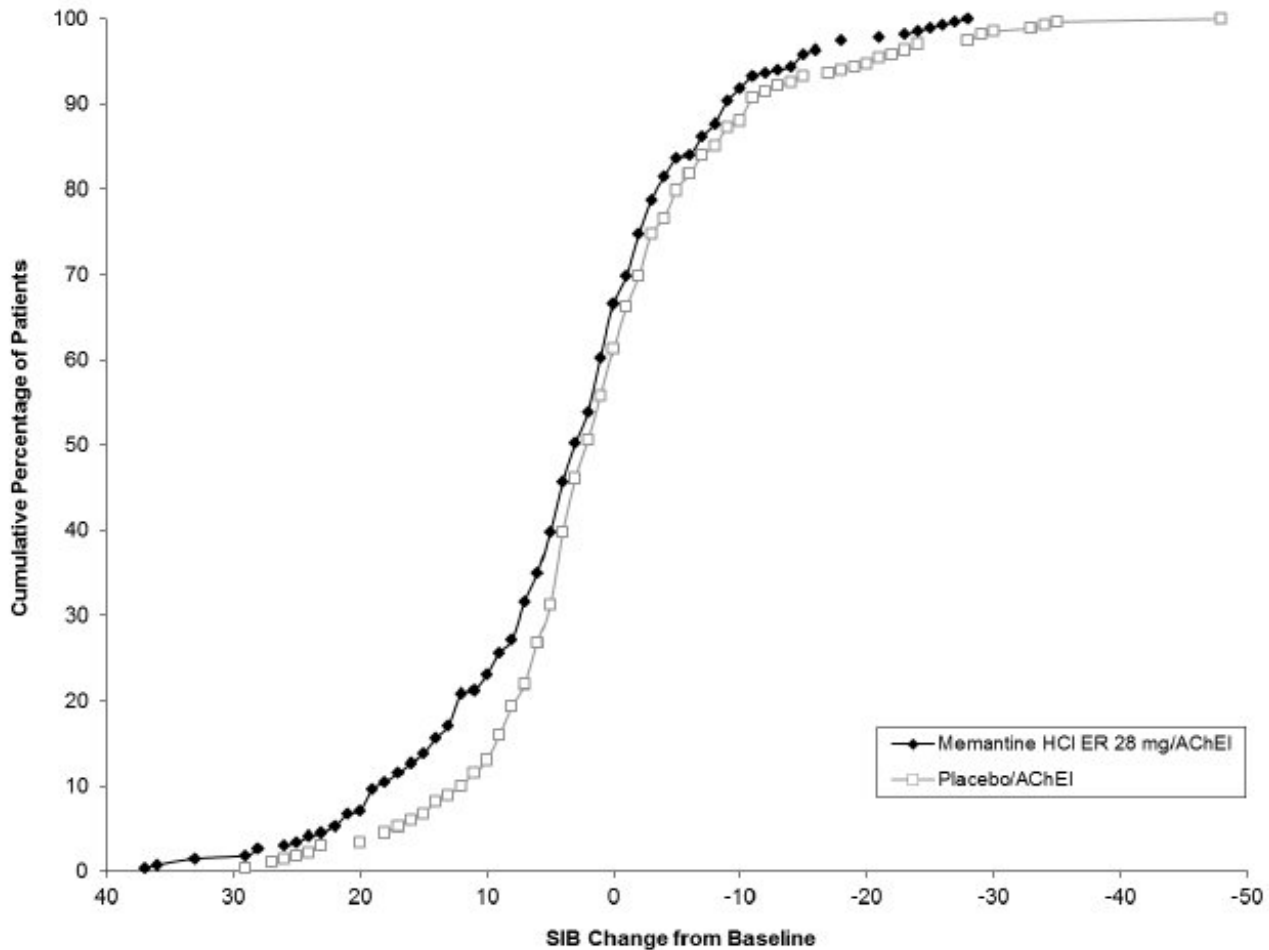


Figure 2: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in SIB scores.

Effects on Severe Impairment Battery (SIB) in the subset of Patients on Concomitant Donepezil Therapy

Approximately 68% of the patients randomized to receive either memantine hydrochloride extended-release 28 mg or placebo were taking donepezil at Baseline and throughout the study. At 24 weeks of treatment, in patients on concomitant donepezil treatment, the mean difference in the SIB change scores for the memantine hydrochloride extended-release 28 mg-treated patients compared to patients on placebo (2.7 units) was similar to that observed for the entire study population (2.6 units).

Effects of Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus)

Figure 3 shows the time course for the CIBIC-Plus score for patients in the two treatment groups completing the 24 weeks of the study. At 24 weeks of treatment, the mean difference in the CIBIC-Plus scores for the memantine hydrochloride extended-release 28 mg/AChEI-treated patients compared to the patients on placebo/AChEI was 0.3 units. Using an LOCF analysis, memantine hydrochloride extended-release 28 mg/AChEI treatment was statistically significantly superior to placebo/AChEI.

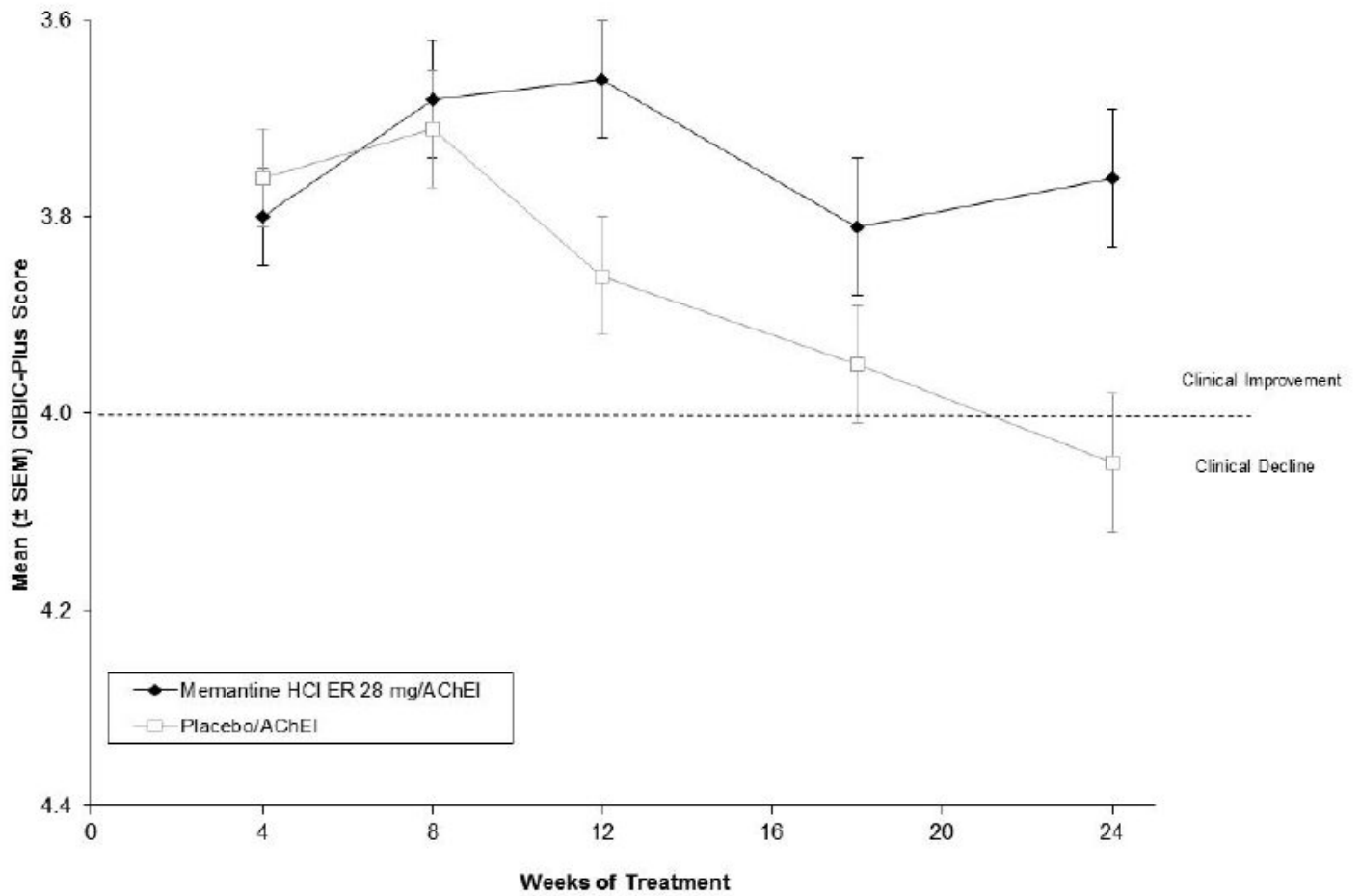


Figure 3: Time course of the CIBIC-Plus score for patients completing 24 weeks of treatment.

Figure 4 is a histogram of the percentage distribution of CIBIC-Plus scores attained by patients assigned to each of the treatment groups who completed 24 weeks of treatment.

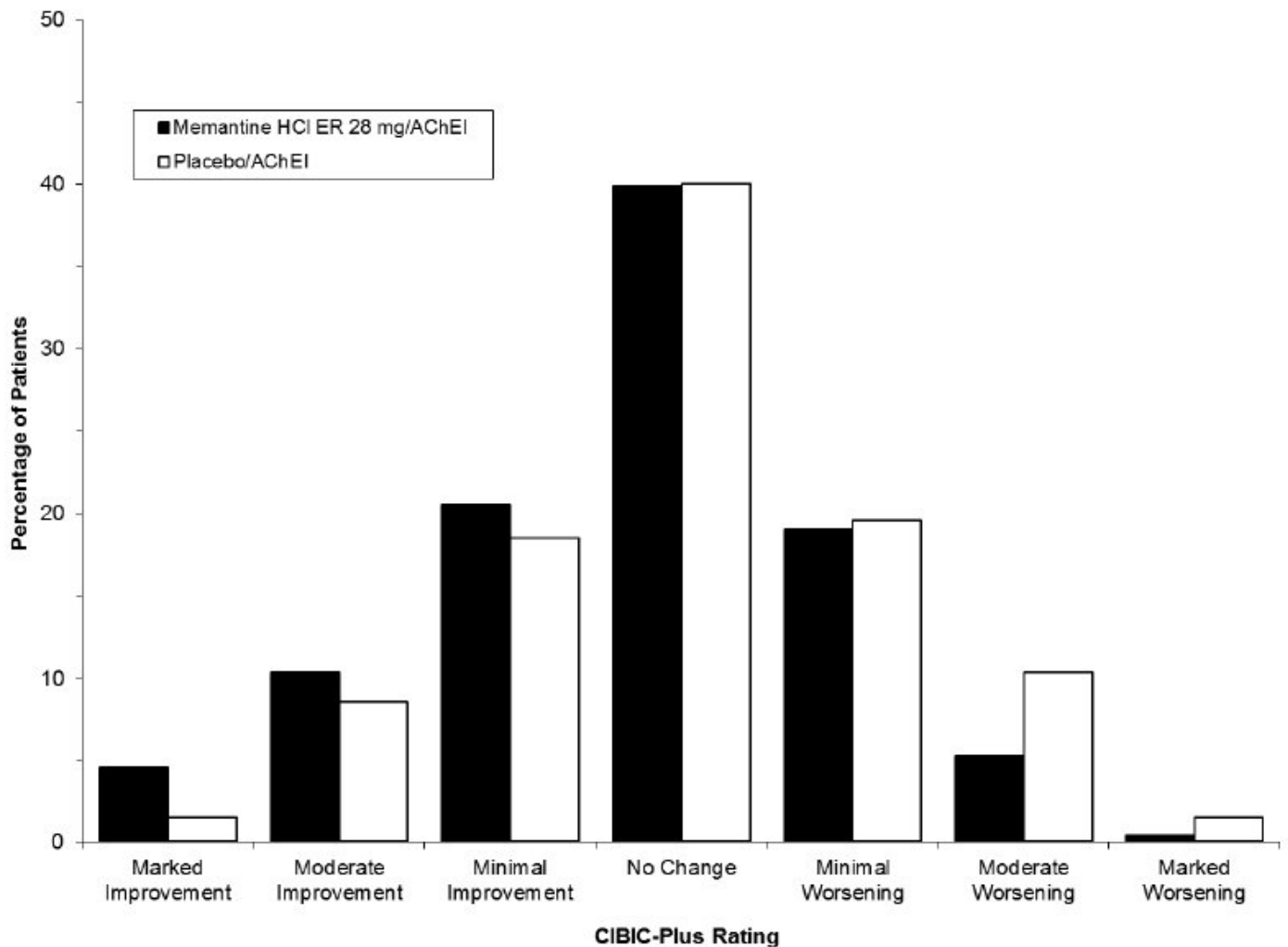


Figure 4: Distribution of CIBIC-Plus ratings at week 24.

Effects on CIBIC-Plus in the Subset of Patients on Concomitant Donepezil Therapy

Approximately 68% of the patients randomized to receive either memantine hydrochloride extended-release 28 mg or placebo were taking donepezil at baseline and throughout the study. At 24 weeks of treatment, in patients on concomitant donepezil, the mean difference in the CIBIC-Plus scores for the memantine hydrochloride extended-release 28 mg-treated patients compared to patients on placebo (0.3 units) was similar to that observed for the entire study population (0.3 units).

Donepezil Hydrochloride

The effectiveness of donepezil hydrochloride as a treatment for patients with severe Alzheimer's disease was based on the results of two double-blind, placebo-controlled trials.

6-Month Study of Donepezil Hydrochloride

This was a randomized, double-blind, placebo-controlled clinical study conducted in Sweden in patients with probable or possible Alzheimer's disease diagnosed by NINCDS-ADRDA and DSM-IV criteria, MMSE: range of 1-10. Two hundred and forty eight (248) patients with severe Alzheimer's disease were randomized to donepezil hydrochloride or placebo. For patients randomized to donepezil hydrochloride, treatment was initiated at

5 mg once daily for 28 days and then increased to 10 mg once daily. At the end of the 6 month treatment period, 90.5% of the donepezil hydrochloride treated patients were receiving the 10 mg/day dose. The mean age of patients was 84.9 years, with a range of 59 to 99. Approximately 77% of patients were women, and 23% were men. Almost all patients were Caucasian. Probable AD was diagnosed in the majority of the patients (83.6% of donepezil hydrochloride treated patients and 84.2% of placebo treated patients).

Study Outcome Measures

The effectiveness of treatment with donepezil hydrochloride was evaluated using a dual outcome assessment strategy that evaluated cognitive function using an instrument designed for more impaired patients and overall function through caregiver-rated assessment. This study showed that patients on donepezil hydrochloride experienced significant improvement on both measures compared to placebo.

The ability of donepezil hydrochloride to improve cognitive performance was assessed with the SIB.

Daily function was assessed using the Modified Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease (ADCS-ADL-severe). The ADCS-ADL-severe is derived from the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory, which is 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 ADCS-ADL-severe is a subset of 19 items, including ratings of the patient's ability to eat, dress, bathe, use the telephone, get around (or travel), and perform other activities of daily living; it has been validated for the assessment of patients with moderate to severe dementia. The ADCS-ADL-severe has a scoring range of 0 to 54, with the lower scores indicating greater functional impairment. The investigator performs the inventory by interviewing a caregiver, in this study a nurse staff member, familiar with the functioning of the patient.

Effects on the SIB

Figure 5 shows the time course for the change from baseline in SIB score for the two treatment groups over the 6 months of the study. At 6 months of treatment, the mean difference in the SIB change scores for donepezil hydrochloride treated patients compared to patients on placebo was 5.9 points. Donepezil hydrochloride treatment was statistically significantly superior to placebo.

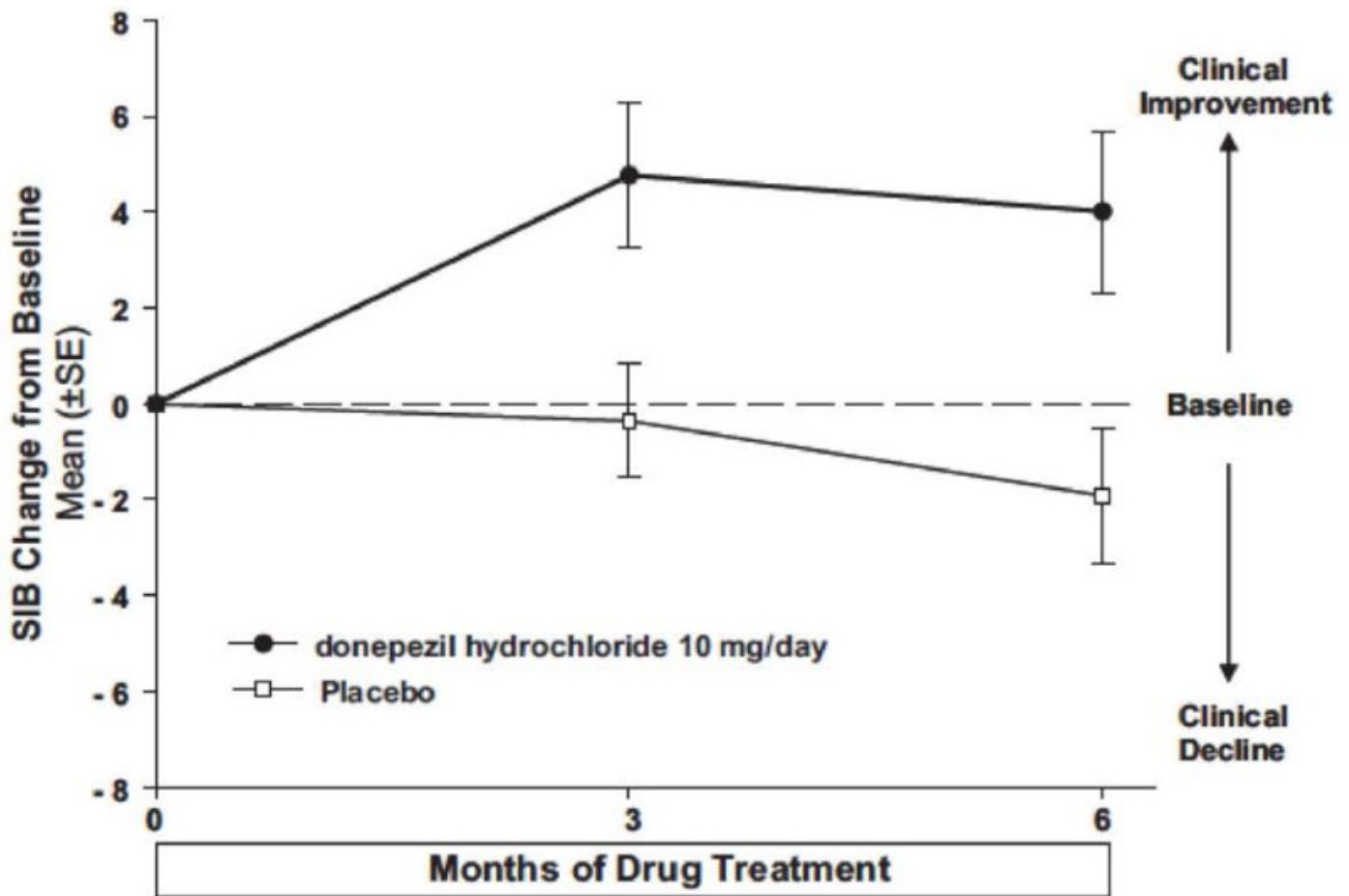


Figure 5. Time Course of the Change from Baseline in SIB Score for Patients Completing 6 months of Treatment.

Figure 6 illustrates the cumulative percentages of patients from each of the two treatment groups who attained the measure of improvement in SIB score shown on the X-axis. While patients assigned both to donepezil hydrochloride and to placebo have a wide range of responses, the curves show that the donepezil hydrochloride group is more likely to show a greater improvement in cognitive performance.

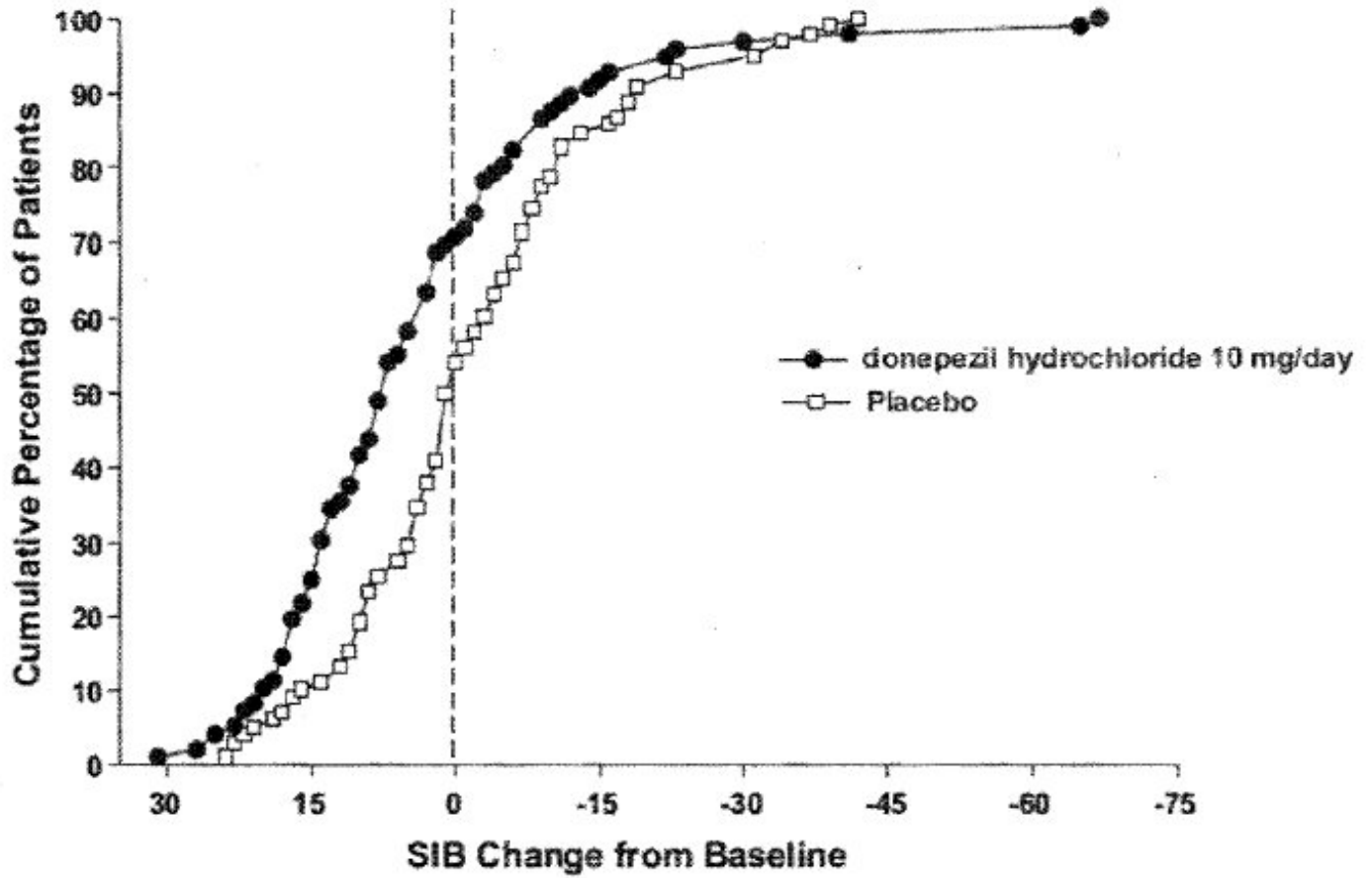


Figure 6. Cumulative Percentage of Patients Completing 6 Months of Double-blind Treatment with Particular Changes from Baseline in SIB Scores.

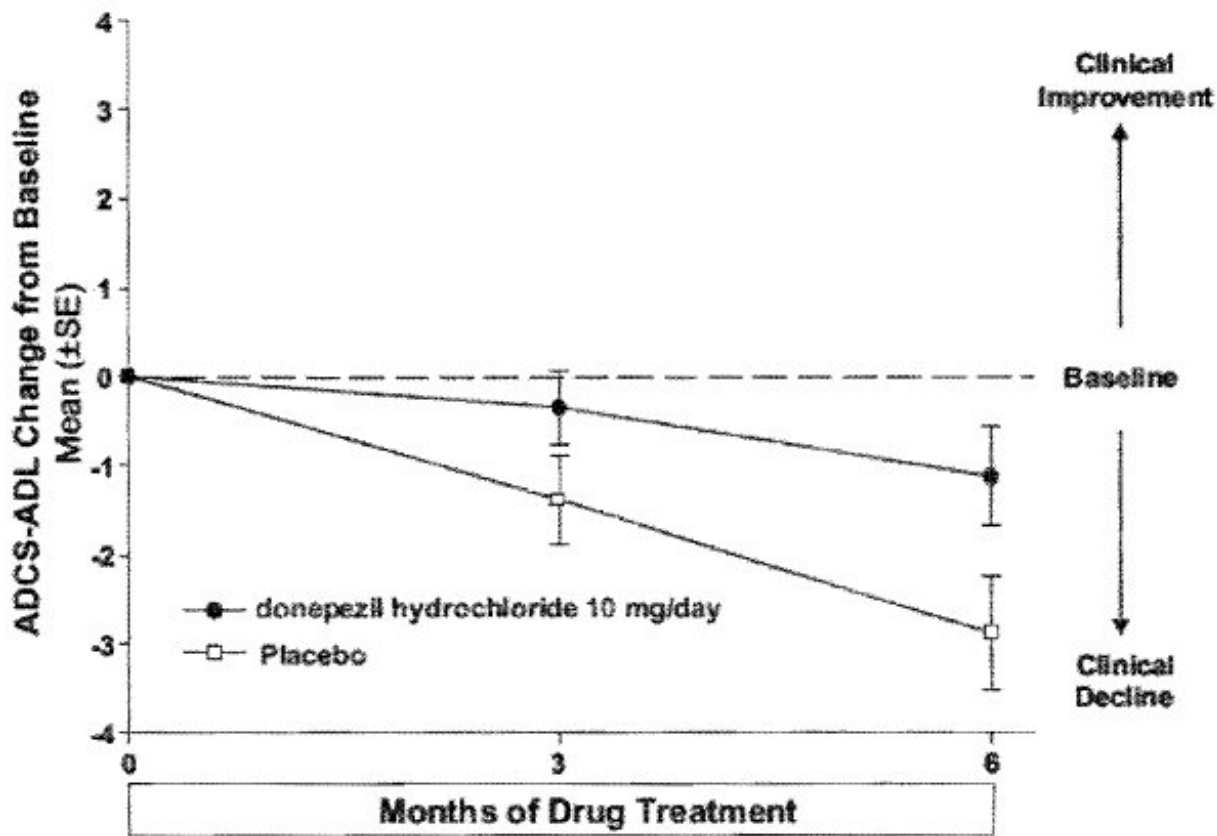


Figure 7. Time Course of the Change from Baseline in ADCS-ADL-Severe Score for Patients Completing 6 Months of Treatment.

Effects on the ADCS-ADL-severe

Figure 7 illustrates the time course for the change from baseline in ADCS-ADL-severe scores for patients in the two treatment groups over the 6 months of the study. After 6 months of treatment, the mean difference in the ADCS-ADL-severe change scores for donepezil hydrochloride treated patients compared to patients on placebo was 1.8 points. Donepezil hydrochloride treatment was statistically significantly superior to placebo.

Figure 8 shows the cumulative percentages of patients from each treatment group with specified changes from baseline ADCS-ADL-severe scores. While both patients assigned to donepezil hydrochloride and placebo have a wide range of responses, the curves demonstrate that the donepezil hydrochloride group is more likely to show a smaller decline or an improvement.

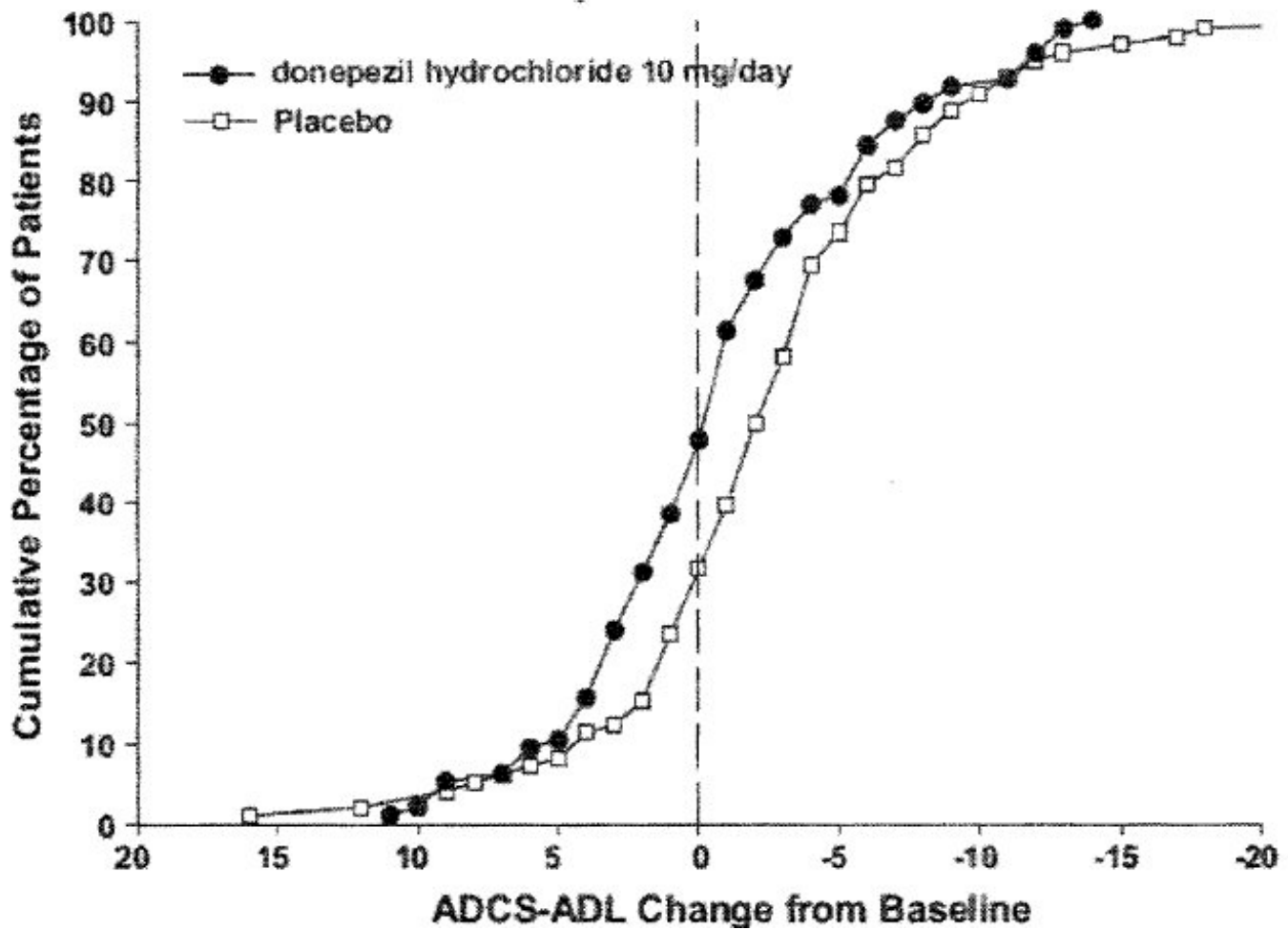


Figure 8. Cumulative Percentage of Patients Completing 6 Months of Double-blind Treatment with Particular Changes from Baseline in ADCS-ADL-Severe Scores.

24-Week Study of Donepezil Hydrochloride

In a randomized, double-blind, placebo-controlled study conducted in Japan, 325 patients with severe Alzheimer's disease received doses of 5 mg/day or 10 mg/day of donepezil hydrochloride, administered once daily, or placebo. Patients randomized to treatment with donepezil hydrochloride were to achieve their assigned doses by titration, beginning at 3 mg/day, and extending over a maximum of 6 weeks. Two hundred and forty eight (248) patients completed the study, with similar proportions of patients completing the study in each treatment group. The primary efficacy measures for this study were the SIB and CIBIC-plus.

At 24 weeks of treatment, statistically significant treatment differences were observed between the 10 mg/day dose of donepezil hydrochloride and placebo on both the SIB and CIBIC-plus. The 5 mg/day dose of donepezil hydrochloride showed a statistically significant superiority to placebo on the SIB, but not on the CIBIC-plus.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Memantine and donepezil hydrochlorides extended-release capsules 21 mg/10 mg, are

hard gelatin capsules, with natural body and natural cap imprinted with the logo A313 on the body and 21/10 on the cap in black ink, containing white to off-white beads and are supplied in:

Bottle of 30: NDC# 62559-207-30

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see *USP Controlled Room Temperature*]. Dispense in a tight, light-resistant container, as defined in the USP.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Dosing Information

- Instruct patients and caregivers to take memantine and donepezil hydrochlorides extended-release capsules only once daily in the evening, as prescribed [see *Dosage and Administration (2.1)*].
- If a patient misses a single dose of memantine and donepezil hydrochlorides extended-release capsules, that patient should not double up on the next dose. The next dose should be taken as scheduled [see *Dosage and Administration (2.1)*].
- Instruct patients and caregivers that memantine and donepezil hydrochlorides extended-release capsules should be swallowed whole. Alternatively, memantine and donepezil hydrochlorides extended-release capsules may be opened and sprinkled on applesauce and the entire contents should be consumed. The capsules should not be divided, chewed, or crushed. Warn patients and caregivers not to use any memantine and donepezil hydrochlorides extended-release capsules that are damaged or show signs of tampering [see *Dosage and Administration (2.2)*].

Common Adverse Reactions

Advise patients and caregivers that memantine and donepezil hydrochlorides extended-release capsules may cause headache, diarrhea, dizziness, anorexia, vomiting, nausea, and ecchymosis [see *Adverse Reactions (6.1)*].

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PATIENT INFORMATION

Memantine and Donepezil Hydrochlorides Extended-Release Capsules

(me-MAN-teen and doe-NEP-e-zil HYE-droe-KLOR-ides Extended-Release Capsules)

What are memantine and donepezil hydrochlorides extended-release capsules?

- Memantine and donepezil hydrochlorides extended-release capsules are a prescription medicine used to treat moderate to severe dementia in people with Alzheimer's disease. Memantine and donepezil hydrochlorides extended-release capsules contain 2 medicines, memantine hydrochloride (HCl), an NMDA receptor antagonist, and donepezil HCl, an acetylcholinesterase inhibitors. Memantine and donepezil hydrochlorides extended-release capsules are for people who are taking donepezil HCl 10 mg.
- It is not known if memantine and donepezil hydrochlorides extended-release capsules are safe and effective in children.

Do not take memantine and donepezil hydrochlorides extended-release capsules if you have an allergy to memantine HCl, donepezil HCl, medicines that contains piperidines, or any of the ingredients in memantine and donepezil hydrochlorides extended-release capsules. See the end of this leaflet for a complete list of ingredients in memantine and donepezil hydrochlorides extended-release capsules.

Before taking memantine and donepezil hydrochlorides extended-release capsules, tell your doctor about all your medical conditions, including if you:

- have heart problems including an irregular, slow, or fast heartbeat.
- have asthma or lung problems.
- have seizures.
- have stomach ulcers.
- have bladder or kidney problems.
- have liver problems.
- have surgical, dental, or other medical procedures scheduled and anesthesia may be used.
- are pregnant or plan to become pregnant. It is not known if memantine hydrochloride and donepezil hydrochloride can harm an unborn baby.
- are breast-feeding or plan to breastfeed. It is not known if memantine hydrochloride and donepezil hydrochloride passes into breast milk. Talk to your doctor about the best way to feed your baby if you take memantine and donepezil hydrochlorides extended-release capsules.

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

How should I take memantine and donepezil hydrochlorides extended-release capsules?

- Take memantine and donepezil hydrochlorides extended-release capsules exactly as your doctor tells you to take it.
- Do not change your dose or stop taking memantine and donepezil hydrochlorides extended-release capsules without talking to your doctor.
- Take memantine and donepezil hydrochlorides extended-release capsules by mouth 1 time each evening before going to bed.
- Take memantine and donepezil hydrochlorides extended-release capsules with or without food.
- Memantine and donepezil hydrochlorides extended-release capsules may be opened and sprinkled on applesauce before swallowing. Sprinkle all of the medicine in the capsule on the applesauce. **Do not** divide the dose.
- If you do not open and sprinkle memantine and donepezil hydrochlorides extended-

release capsules on applesauce, the memantine and donepezil hydrochlorides extended-release capsules must be swallowed whole. **Do not** divide, chew, or crush memantine and donepezil hydrochlorides extended-release capsules.

- If you miss a dose take memantine and donepezil hydrochlorides extended-release capsules at your next scheduled dose. **Do not** take **2** doses of memantine and donepezil hydrochlorides extended-release capsules at the same time.
- **Do not** use any memantine and donepezil hydrochlorides extended-release capsules that are damaged or show signs of tampering.
- If you take too much memantine and donepezil hydrochlorides extended-release capsules, call Poison control center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are the possible side effects of memantine and donepezil hydrochlorides extended-release capsules?

Memantine and donepezil hydrochlorides extended-release capsules may cause serious side effects, including:

- **muscle problems if you need anesthesia**
- **slow heartbeat and fainting.** This happens more often in people with heart problems. Call the doctor right away if the patient faints while taking memantine and donepezil hydrochlorides extended-release capsules.
- **more stomach acid.** This raises the chance of ulcers and bleeding especially when taking memantine and donepezil hydrochlorides extended-release capsules. The risk is higher for patients who had ulcers, or take aspirin or other NSAIDs.
- **nausea and vomiting**
- **difficulty passing urine**
- **seizures**
- **worsening of lung problems** in people with asthma or other lung disease.

The most common side effects of memantine HCl include:

-
- headache
 - diarrhea
 - dizziness
-

The most common side effects of donepezil HCl include:

-
- diarrhea
 - not wanting to eat (anorexia)
 - bruising
-

These are not all the possible side effects of memantine and donepezil hydrochlorides extended-release capsules.

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 and donepezil hydrochlorides extended-release capsules?

Store memantine and donepezil hydrochlorides extended-release capsules at room temperature, about 68°F and 77°F (20°C to 25°C). Capsules should be stored in the original prescription container or other light resistant container.

General information about the safe and effective use of memantine and donepezil hydrochlorides extended-release capsules

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use memantine and donepezil hydrochlorides extended-release capsules for a condition for which it was not prescribed. Do not give memantine and donepezil hydrochlorides extended-release capsules to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about memantine and donepezil hydrochlorides extended-release capsules that is written for health professionals.

What are the ingredients in memantine and donepezil hydrochlorides extended-release capsules?

Active ingredient: memantine hydrochloride and donepezil hydrochloride

Inactive ingredients: colloidal silicon dioxide, ethylcellulose, hydroxypropyl cellulose, hypromellose, polyethylene glycol, sugar spheres (consisting of sugar syrup, corn starch, and sucrose) and talc. The hard gelatin capsules contain black iron oxide and gelatin.

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

Rx only

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PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

NDC 62559-207-30

Memantine and Donepezil Hydrochlorides Extended-Release Capsules

21 mg/10 mg

Rx only

30 Capsules

NDC 62559-207-30

**Memantine and
Donepezil
Hydrochlorides
Extended-Release
Capsules**

21 mg/10 mg



Rx only
30 Capsules

Each capsule contains 21 mg of memantine HCl extended-release and 10 mg donepezil HCl

Usual Dosage: Take 1 capsule once daily, see package insert for full Prescribing Information.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Protect from moisture.

Dispense in a tight, light-resistant container as defined in the USP.

**KEEP THIS AND ALL MEDICATION
OUT OF THE REACH OF CHILDREN.**

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10772 Rev 11/24



GTIN 00362559207300



SN: A123456789
LOT: A12345
EXP: YYYY/MM

MEMANTINE AND DONEPEZIL HYDROCHLORIDES

memantine and donepezil hydrochlorides capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:62559-207
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MEMANTINE HYDROCHLORIDE (UNII: JY0WD0UA60) (MEMANTINE - UNII:W8O17SJF3T)	MEMANTINE HYDROCHLORIDE	21 mg
DONEPEZIL HYDROCHLORIDE (UNII: 3O2T2PJ89D) (DONEPEZIL - UNII:8SSC91326P)	DONEPEZIL HYDROCHLORIDE	10 mg

Inactive Ingredients

Ingredient Name	Strength
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
HYDROXYPROPYL CELLULOSE (90000 WAMW) (UNII: UKE75GEA7F)	
TALC (UNII: 7SEV7J4R1U)	
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
ETHYLCELLULOSE AQUEOUS DISPERSION TYPE B (UNII: HZJ2V81RYU)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
SHELLAC (UNII: 46N107B71O)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSO FERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

Color	WHITE (clear/natural)	Score	no score
Shape	CAPSULE	Size	18mm
Flavor		Imprint Code	A313;21;10
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:62559-207-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2025	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA208237	01/01/2025	

Labeler - ANI Pharmaceuticals, Inc. (145588013)

Revised: 1/2025

ANI Pharmaceuticals, Inc.