

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 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

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 maximum recommended human dose (MRHD of 28 mg/day) 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 hydrochloride extended-release capsules as a treatment for patients with moderate to severe Alzheimer's disease was based on the results of a double-blind, placebo-controlled trial.

24-week Study of Memantine Hydrochloride Extended-Release Capsules

This was a randomized double-blind clinical investigation in 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 \geq 3 and \leq 14 at Screening and Baseline) receiving acetylcholinesterase inhibitor (AChEI) therapy at a stable dose for 3 months prior to screening. The mean age of patients participating in this trial was 76.5 years with a range of 49 to 97 years. Approximately 72% of patients were female and 94% were Caucasian.

Study Outcome Measures

The effectiveness of memantine hydrochloride extended-release capsules were 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 capsules 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 capsules 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 capsules 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 capsules 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 capsules 28 mg/AChEI treatment was statistically significantly superior to placebo/AChEI.

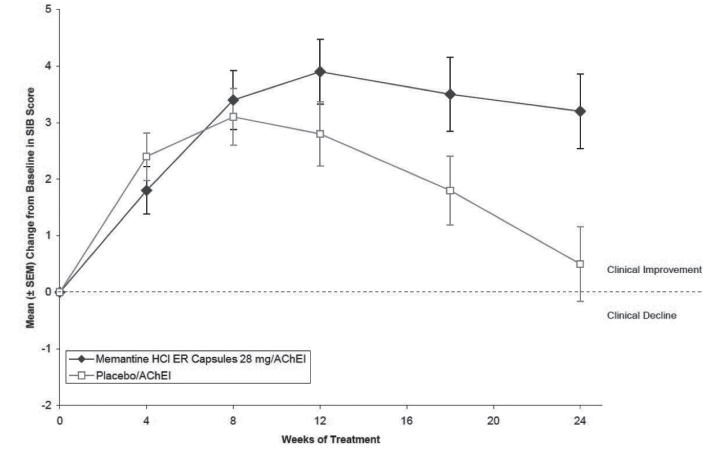


Figure 1: Time course of the change from baseline in SIB score for patients completing 24 weeks of treatment.

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 capsules

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

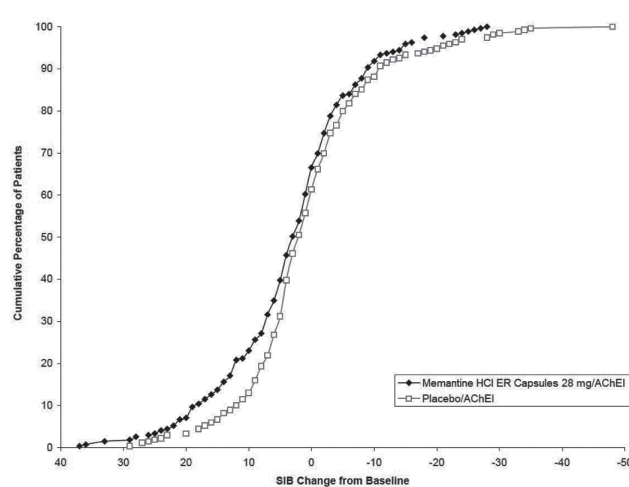


Figure 2: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in SIB scores.

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 capsules 28 mg/AChEI-treated patients compared to the patients on placebo/AChEI was 0.3 units. Using an LOCF analysis, memantine hydrochloride extended-release capsules 28 mg/AChEI treatment was statistically significantly superior to placebo/AChEI.

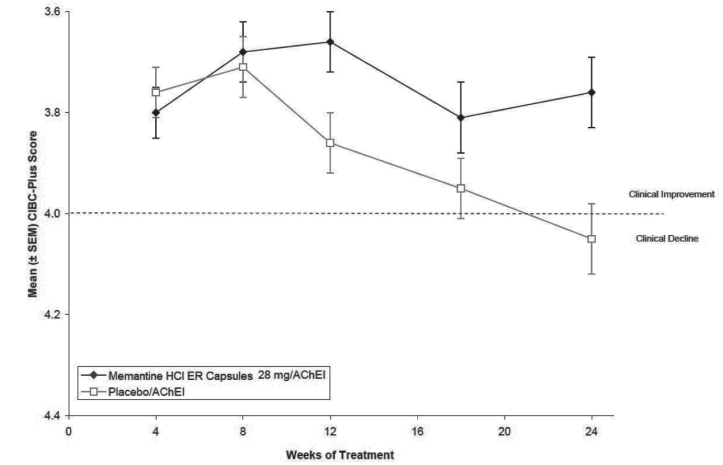


Figure 3: Time course of the CIBIC-Plus score for patients completing 24 weeks of treatment.

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.

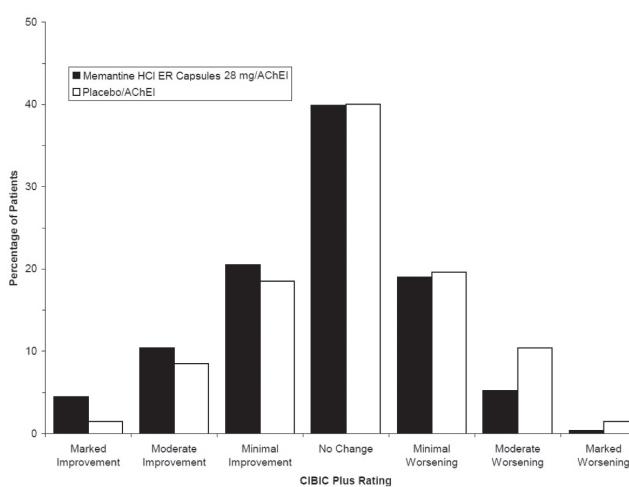


Figure 4: Distribution of CIBIC-Plus ratings at week 24.

16 HOW SUPPLIED/STORAGE AND HANDLING

The 7 mg, capsule is available as a Size 4CS hard gelatin capsule with a yellow opaque cap and yellow opaque body, imprinted with "par" on the cap and "C346" on the body in black ink, containing white to off-white spherical-shaped film-coated pellets. Bottle of 30.....NDC# 10370-346-11

The 14 mg, capsule is available as a Size 4CS hard gelatin capsule with a green opaque cap and yellow opaque body, imprinted with "par" on the cap and "C347" on the body in black ink, containing white to off-white spherical-shaped film-coated pellets. Bottle of 30.....NDC# 10370-347-11
Bottle of 90.....NDC# 10370-347-09

The 21 mg, capsule is available as a Size 3CS hard gelatin capsule with a green opaque cap and white opaque body, imprinted with "par" on the cap and "C348" on the body in black ink, containing white to off-white spherical-shaped film-coated pellets. Bottle of 30.....NDC# 10370-348-11

The 28 mg, capsule is available as a Size 2CS hard gelatin capsule with green opaque cap and green opaque body, imprinted with "par" on the cap and "C349" on the body in black ink, containing white to off-white spherical-shaped film-coated pellets.

Bottle of 30.....NDC# 10370-349-11

Bottle of 90.....NDC# 10370-349-09

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

17 PATIENT COUNSELING INFORMATION

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

- To assure safe and effective use of memantine hydrochloride extended-release capsules, the information and instructions provided in the patient information section should be discussed with patients and caregivers.
- Instruct patients and caregivers to take memantine hydrochloride extended-release capsules only once per day, as prescribed.
- Instruct patients and caregivers that memantine hydrochloride extended-release capsules be swallowed whole. Alternatively, memantine hydrochloride 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 not to use any memantine hydrochloride extended-release capsules that are damaged or show signs of tampering.
- If a patient misses a single dose of memantine hydrochloride extended-release capsules, 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 extended-release capsules for several days, dosing should not be resumed without consulting that patient's healthcare professional.
- Advise patients and caregivers that memantine hydrochloride extended-release capsules may cause headache, diarrhea, and dizziness.

Patient Information

Memantine Hydrochloride [me man' teen hye dro klo'ride] Extended-Release Capsules

Read this Patient Information that comes with memantine hydrochloride extended-release capsules 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 are memantine hydrochloride extended-release capsules?

Memantine hydrochloride extended-release capsules are a prescription medicine used for the treatment of moderate to severe dementia in people with Alzheimer's disease. Memantine hydrochloride extended-release capsules belong to a class of medicines called NMDA (N-methyl-D-aspartate) inhibitors.

It is not known if memantine hydrochloride extended-release capsules are safe and effective in children.

Who should not take memantine hydrochloride extended-release capsules?

Do not take memantine hydrochloride extended-release capsules if you are allergic to memantine or any of the other ingredients in memantine hydrochloride extended-release capsules. See the end of this leaflet for a complete list of ingredients in memantine hydrochloride extended-release capsules.

What should I tell my doctor before taking memantine hydrochloride extended-release capsules? Before you take memantine hydrochloride extended-release capsules, 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 extended-release capsules will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if memantine hydrochloride extended-release capsules pass into your breast milk. You and your doctor should decide if you will take memantine hydrochloride extended-release capsules or breastfeed.

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

Taking memantine hydrochloride extended-release capsules with certain other medicines may affect each other. Taking memantine hydrochloride extended-release capsules 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 extended-release capsules?

- Your doctor will tell you how much memantine hydrochloride extended-release capsules to take and when to take it.
- Your doctor may change your dose if needed.
- Memantine hydrochloride extended-release capsules may be taken with food or without food.
- Memantine hydrochloride extended-release capsules may be opened and sprinkled on applesauce before swallowing, but the contents of the entire capsule should be taken and the dose should not be divided. Except when opened and sprinkled on applesauce, memantine hydrochloride extended-release capsules must be swallowed whole and never crushed, divided or chewed.
- Do not use any memantine hydrochloride extended-release capsules that are damaged or show signs of tampering.
- If you are currently taking another formulation of memantine, talk to your healthcare professional about how to switch to memantine hydrochloride extended-release capsules.
- If you forget to take one dose of memantine hydrochloride extended-release capsules, 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 extended-release capsules for several days, you should not take the next dose until you talk to your doctor.
- If you take too much memantine hydrochloride extended-release capsules, 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 extended-release capsules?

Memantine hydrochloride extended-release capsules may cause side effects, including:

The most common side effects of memantine hydrochloride extended-release capsules include:

- headache
- diarrhea
- dizziness

These are not all the possible side effects of memantine hydrochloride extended-release capsules. 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 extended-release capsules?

- Store memantine hydrochloride extended-release capsules at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

What are the ingredients in memantine hydrochloride extended-release capsules?

Active ingredient: memantine hydrochloride

Inactive ingredients: sucrose, corn starch, hydroxypropyl cellulose, talc, ethylcellulose, triethyl citrate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, gelatin, shellac, iron oxide black, FD&C Blue # 2, FD&C Red # 40, D&C Yellow # 10, FD&C Blue # 1 and FD&C Yellow # 6. In addition, the 14 mg, 21 mg and 28 mg hard gelatin capsules contain the colorant FD&C Green # 3.

Keep memantine hydrochloride extended-release capsules and all medicines out of the reach of children.

General information about the safe and effective use of memantine hydrochloride extended-release capsules:

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not take memantine hydrochloride extended-release capsules for a condition for which it was not prescribed. Do not give memantine hydrochloride extended-release capsules 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 extended-release capsules. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about memantine hydrochloride extended-release capsules that was written for healthcare professionals.

For more information about memantine hydrochloride extended-release capsules or to report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Manufactured by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

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