

antihyperglycemic drug Glucovance® (glyburide and metformin HCl) 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Memantine produced no evidence of genotoxic potential when evaluated in the *in vitro* *S. typhimurium* or *E. coli* reverse mutation assay, an *in vivo* 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 equivalent to an *in vitro* gene mutation assay using Chinese hamster V79 cells.

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

13.2 Animal Toxicology and/or Pharmacology

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 neocortex 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 6 times the maximum recommended human dose of 20 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 as a treatment for patients with moderate to severe Alzheimer's disease was demonstrated in 2 randomized, double-blind, placebo-controlled clinical studies (Studies 1 and 2) conducted in the United States that assessed both cognitive function and day to day function. The mean age of patients participating in these two trials was 76 with a range of 50 to 83 years. Approximately 65% of patients were female and 91% of patients were Caucasian. A third study (Study 3), carried out in Latvia, enrolled patients with severe dementia, but did not assess cognitive function as a planned endpoint. Study Outcome Measures: In each U.S. study, the effectiveness of memantine hydrochloride was determined using both an instrument designed to evaluate overall function through caregiver-related assessment, and an instrument that measures cognition. Both studies showed that patients on memantine hydrochloride experienced significant improvement on both measures compared to placebo.

Day-to-day function was assessed in both studies using the modified Alzheimer's disease Cooperative Study - Activities of Daily Living inventory (ADCS-ADL). The ADCS-ADL consists of a comprehensive battery of ADL questions used to measure the functional capabilities of patients. Each ADL item is rated from the highest level of independent performance to complete loss. The investigator performs the inventory by interviewing a caregiver familiar with the behavior of the patient. A subset of 10 items, including ratings of the patient's ability to eat, dress, bathe, telephone, travel, shop, and perform other household chores has been validated for the assessment of patients with moderate to severe dementia. This is the modified ADCS-ADL, which has a scoring range of 0 to 54, with the lower scores indicating greater functional impairment.

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

Study 1 (Twenty-Eight-Week Study)

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

Effects on the ADCS-ADL

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

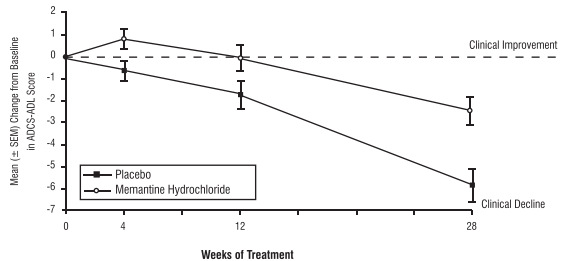


Figure 1: Time course of the change from baseline in ADCS-ADL score for patients completing 28 weeks of treatment.

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

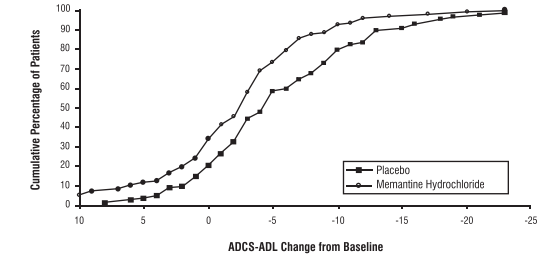


Figure 2: Cumulative percentage of patients completing 28 weeks of double-blind treatment with specified changes from baseline in ADCS-ADL scores.

Effects on the SIB

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

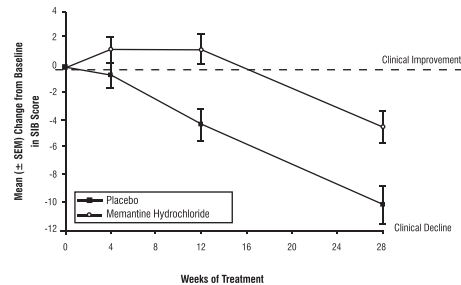


Figure 3: Time course of the change from baseline in SIB score for patients completing 28 weeks of treatment.

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

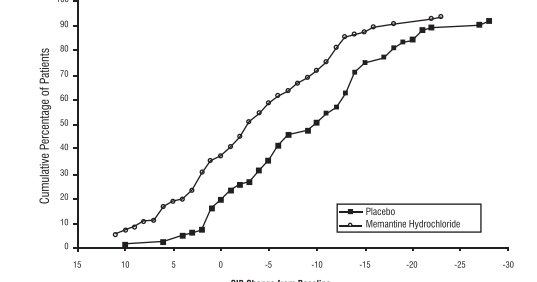


Figure 4: Cumulative percentage of patients completing 28 weeks of double-blind treatment with specified changes from baseline in SIB scores.

Study 2 (Twenty-Four-Week Study)

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

Effects on the ADCS-ADL

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

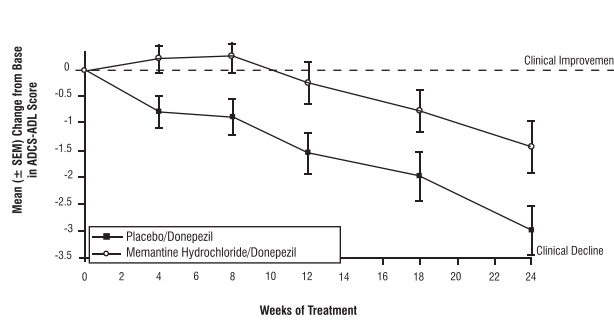


Figure 5: Time course of the change from baseline in ADCS-ADL score for patients completing 24 weeks of treatment.

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

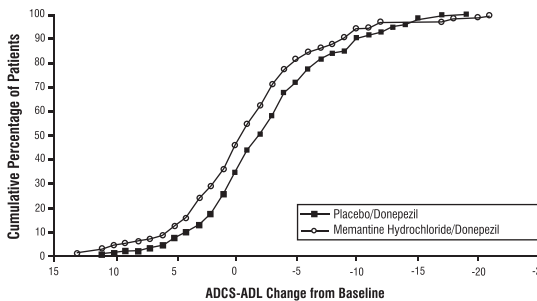


Figure 6: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in ADCS-ADL scores.

Effects on the SIB

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

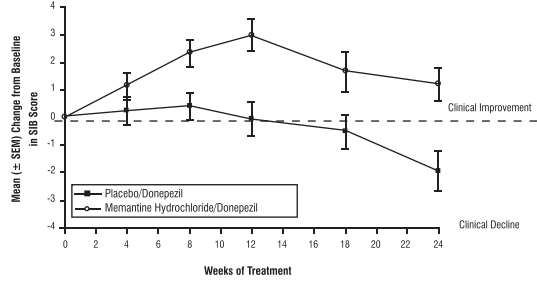


Figure 7: Time course of the change from baseline in SIB score for patients completing 24 weeks of treatment.

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

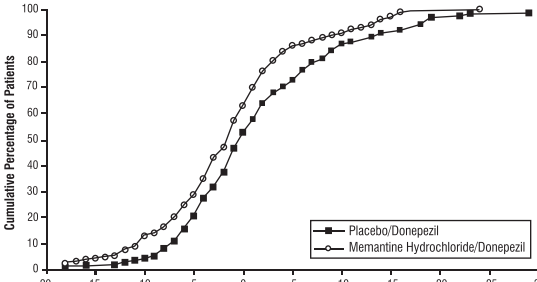


Figure 8: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in SIB scores.

Study 3 (Twelve-Week Study)

In a double-blind study of 12 weeks duration, conducted in nursing homes in Latvia, 156 patients with dementia according to DSM-IV-R, a Mini-Mental State Examination score of < 10 , and Global Deterioration Scale staging of 5 to 7 were randomized to either memantine hydrochloride or placebo. For patients randomized to memantine hydrochloride, treatment was initiated at 5 mg once daily and increased to 10 mg once daily after 1 week. The primary efficacy measures were the care dependency subscale of the Behavioral Rating Scale for Geriatric Patients (BRGP), a measure of day-to-day function, and a Clinical Global Impression of Change (CGIC), a measure of overall clinical effect. No valid measure of cognitive function was used in this study. A statistically significant treatment difference at 12 weeks that favored memantine hydrochloride over placebo was seen on both primary efficacy measures. Because the patients entered were a mixture of Alzheimer's disease and vascular dementia, an attempt was made to distinguish the two groups and all patients were later designated as having either vascular dementia or Alzheimer's disease, based on their scores on the Hachinski Ischemic Scale at study entry. Only about 50% of the patients had computerized tomography of the brain. For the subset designated as having Alzheimer's disease, a statistically significant treatment effect favoring memantine hydrochloride over placebo at 12 weeks was seen on both the BRGP and CGIC.

16 HOW SUPPLIED/STORAGE AND HANDLING

Memantine Hydrochloride Tablets, USP 5 mg: Tan colored, capsule-shaped, film-coated tablets debossed with "M5" on one side and plain on the other side.

NDC #	Product	Pack Size
64380-774-01	Memantine Hydrochloride Tablets USP 5 mg	1 x 10 Unit Dose
64380-774-30		10 x 10 Unit Dose
64380-774-03		60's bottle
64380-745-30	Memantine Hydrochloride Tablets USP, 10 mg	10 x 10 Unit Dose
64380-745-03		60's bottle

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

To assure safe and effective use of memantine hydrochloride tablets, the following information provided in the patient information section should be discussed with patients and caregivers.

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

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

Manufactured by:
Strides Shasun Limited
Bengaluru - 562106, India

Distributed by:
Strides Pharma Inc.
East Brunswick, NJ 08816

Revised: 05/2017

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Revised: 05/2017

What are the possible side effects of memantine hydrochloride tablets?

Memantine hydrochloride tablets may cause side effects, including:

- dizziness
- confusion
- headache
- constipation

These are not all the possible side effects of memantine hydrochloride tablets. 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 tablets?

- Store memantine hydrochloride tablets at room temperature between 59°F to 77°F (15°C to 30°C).

What are the ingredients in memantine hydrochloride tablets?

Active ingredients: memantine hydrochloride
Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, talc and magnesium stearate
Inactive ingredients for tablet film coating: Memantine hydrochloride tablets USP 5 mg are coated with opadry orange (hypromellose, titanium dioxide, polyethylene glycol, FD&C yellow #6 and FD&C blue #2) and memantine hydrochloride tablets USP 10 mg are coated with opadry grey (hypromellose, titanium dioxide, polyethylene glycol and black iron oxide).

Keep memantine hydrochloride tablets and all medicines out of the reach of children.

General information about the safe and effective use of memantine hydrochloride tablets.

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

For more information about memantine hydrochloride tablets, go to www.strideshasun.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch or call Strides Pharma Inc. at 1-877-244-9825.

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

Manufactured by:
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Revised: 05/2017

1034766

Perporation required.

Back side



0812

360 x 420mm

ARTWORK DETAIL LABEL

Product	Memantine HCl Tablets		
Buyer/Country	STRIDES PHARMA INC.	Component	Out sert with medication Guide
Dimension	360 X 420 mm with Perforation as indicated.		Pack NA
New Item Code	1034766	Old Item Code	NA
Colour Shades	BLACK		No. of Colours 1

Change Control No.	NA	Artwork Version	1.0
Design/Style	Front & Back Printing. To be supplied in folded size of 33 mm x 33mm		
Substrate	40 / 45 GSM Paper.		
Special Instructions	PRINTING CLARITY TO BE CLEAR AND SHARP.		
Autocartanator Requirements	NA		

Caution to the printer: Before processing, please ensure that the ARTWORK received for printing is exactly in line with APPROVED ARTWORK provided to you. In case of any FONTS/DESIGN are Mis-matching with the APPROVED ARTWORK, please inform PDC for further action. **DO NOT MAKE ANY CHANGE TO THE ARTWORK WITHOUT WRITTEN INSTRUCTIONS FROM PDC.**