

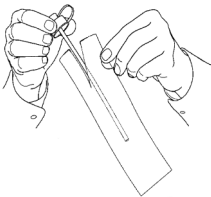
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PATIENT INSTRUCTIONS FOR NAMENDA® Oral Solution

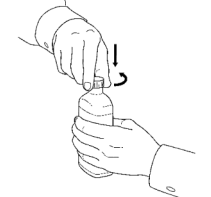
Follow the directions below to use your Namenda® Oral Solution dosing device.

IMPORTANT: Read these instructions before using Namenda® Oral Solution.

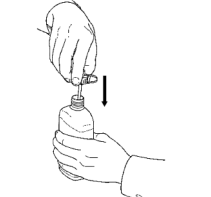
1. Remove oral dosing syringe along with the green cap and plastic tube from its protective plastic bag. Attach the tube to the green cap if it isn't already attached.



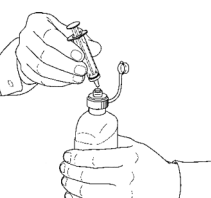
2. The bottle comes with a child-resistant cap. Open it by pushing down on the cap while turning the cap counter-clockwise (to the left). Remove the unscrewed cap. Carefully remove the seal from the bottle and discard.



3. Insert the plastic tube fully into the bottle and screw the green cap tightly onto the bottle by turning the cap clockwise (to the right).

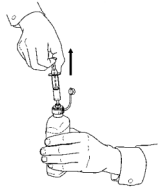


4. The green cap has an attached lid which is to be used for sealing the product in between doses. Keeping the bottle upright on the table, remove the lid to uncover the opening on the top of the cap. With the plunger fully depressed, insert the tip of syringe firmly into the opening in the cap.

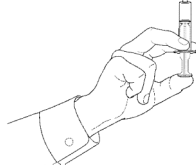


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5. While holding the syringe, gently pull the plunger of the syringe up to draw medicine into the syringe.



6. Remove the syringe from the opening of the cap. Invert the syringe (point tip upwards) and slowly press the plunger to a level that pushes out any large air bubbles that may be present. Keep the plunger in this position. Do not worry about a few tiny bubbles. This will not affect your dose in any way.



7. Re-insert the tip of the syringe into the opening of the cap. While holding the syringe, continue to gently pull out the plunger until the bottom of the black ring of the plunger reaches the appropriate mark on the syringe that corresponds to the dose prescribed.



8. Remove the syringe from the bottle and swallow the Oral Solution directly from the syringe. Do not mix with any other liquid.



9. After use, reseal the bottle by snapping the attached lid closed.



10. Rinse the empty syringe by inserting the open end of the syringe into a glass of water, pulling the plunger out to draw in water, and pushing the plunger in to remove the water. Repeat several times. Allow the syringe to air dry.



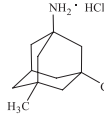
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Namenda® Tablets/Oral Solution (mementine hydrochloride) Rx Only

DESCRIPTION

Namenda® (mementine hydrochloride) is an orally active NMDA receptor antagonist. The chemical name for mementine hydrochloride is 1-amino-3,5-dimethyladamantane hydrochloride with the following structural formula:



The molecular formula is C₁₇H₂₃N·HCl and the molecular weight is 275.76.

Mementine HCl occurs as a fine white to off-white powder and is soluble in water. Namenda is available as tablets or as an oral solution. Namenda is available for oral administration as capsule-shaped, film-coated tablets containing 5 mg and 10 mg of mementine hydrochloride. The tablets also contain the following inactive ingredients: microcrystalline cellulose/colloidal silicon dioxide, talc, croscarmellose sodium, and magnesium stearate. In addition to the following inactive ingredients are also present as components of the film coat: hydroxypropylcellulose, titanium dioxide, polyethylene glycol 400, FD&C yellow #6 and FD&C blue #2 (5 mg tablets), and hydroxypropylcellulose, titanium dioxide, macrogol/polyethylene glycol 400 and iron oxide black (10 mg tablets). Namenda oral solution contains mementine hydrochloride in a strength equivalent to 5 mg of mementine hydrochloride in each mL. The oral solution also contains the following inactive ingredients: sorbitol solution (70%), methyl paraben, propylparaben, propylene glycol, glycerin, natural peppermint flavor #104, citric acid, sodium citrate, and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action and Pharmacodynamics

Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Mementine 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 mementine prevents or slows neurodegeneration in patients with Alzheimer's disease. Mementine showed low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine and glycine receptors and for voltage-dependent Ca²⁺, Na⁺ or K⁺ channels. Mementine also showed antagonistic effects at the 5HT₂ receptor with a potency similar to that for the NMDA receptor and blocked nicotinic acetylcholine receptors with one-tenth to one-fifth the potency.

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

Pharmacokinetics

Mementine is well absorbed after oral administration and has linear pharmacokinetics over the therapeutic dose range. It is excreted predominantly in the urine, unchanged, and has a terminal elimination half-life of about 60-80 hours.

Absorption and Distribution

Following oral administration mementine is highly absorbed with peak concentrations reached in about 3-7 hours. Food has no effect on the absorption of mementine. The mean volume of distribution for mementine is 9-11 L/kg and the plasma protein binding is low (45%).

Metabolism and Elimination

Mementine undergoes partial hepatic metabolism. 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 mementine, and 1-methoxy mementine. The mean volume of distribution of administered dose is excreted as the sum of the parent drug and the N-glucuronide conjugate. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of mementine. Mementine has a terminal elimination half-life of about 60-80 hours. Renal clearance involves active tubular secretion moderated by pH dependent tubular reabsorption.

Special Populations

Renal Impairment: Mementine pharmacokinetics were evaluated following single oral administration of 20 mg mementine HCl 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-∞} 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. No dosage adjustment is recommended for patients with mild and moderate renal impairment. Dosage should be reduced in patients with severe renal impairment (See DOSAGE AND ADMINISTRATION).

Elderly: The pharmacokinetics of Namenda in young and elderly subjects are similar.

Gender: Following multiple dose administration of Namenda 20 mg b.i.d., females had about 45% higher exposure than males. However, there was no difference in exposure when body weight was taken into account.

Drug-Drug Interactions

Substrates of Microsomal Enzymes: *In vitro* studies indicated that at concentrations exceeding those associated with efficacy, mementine does not induce the cytochrome P450 isozymes CYP1A2, CYP2C9, CYP2C19 and CYP3A4/5. In addition, *in vitro* studies have shown that mementine produces minimal inhibition of CYP450 enzymes CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4. These data indicate that no pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Inhibitors of Microsomal Enzymes: Since mementine undergoes minimal metabolism, with the majority of the dose excreted unchanged in urine, an interaction between mementine and drugs that are inhibitors of CYP450 enzymes is unlikely. Coadministration of Namenda with the AChE inhibitor donepezil HCl does not affect the pharmacokinetics of either compound.

Drugs Eliminated via Renal Mechanisms: Mementine is eliminated in part by tubular secretion. *In vivo* studies have shown that multiple doses of the diuretic hydrochlorothiazide/triamterene (HCTZ/TA) did not affect the AUC of mementine at steady state. Mementine did not affect the bioavailability of TA, and decreased AUC and C_{max} of HCTZ by about 20%. Coadministration of mementine with the antihyperglycemic drug glimepiride (glimepiride and metformin) did not affect the pharmacokinetics of mementine, metformin and glimepiride. Mementine did not modify the serum glucose lowering effects of Glucovance®, indicating the absence of a pharmacodynamic interaction.

Drugs that make the urine alkaline: The clearance of mementine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline state may lead to an accumulation of the drug with a possible increase in adverse effects. Drugs that alkalinize the urine (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) would be expected to reduce renal elimination of mementine.

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

CLINICAL TRIALS

The effectiveness of Namenda (mementine hydrochloride) as a treatment for patients with moderate to severe Alzheimer's disease was demonstrated in 2 randomized, double-blind, placebo-controlled clinical studies (Studies 1 and 2) conducted in the United States that assessed both cognitive function and day to day function. The mean age of patients participating in these two trials was 76 with a range of 50-93 years. Approximately 66% of patients were female and 91% of patients were Caucasian.

A third study (Study 3), carried out in Latvia, enrolled patients with severe dementia, but did not assess cognitive function as a planned endpoint. Study Outcome Measures: In each U.S. study, the effectiveness of Namenda 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 Namenda experienced significant improvement on both measures compared to placebo.

Day-to-day function was assessed in both studies using the modified Alzheimer's Disease Cooperative Study - Activities of Daily Living inventory (ADCS-ADL). The ADCS-ADL consists of a comprehensive battery of ADL questions used to measure the functional capabilities of patients. Each ADL item is rated from the highest level of independent performance to complete loss. The investigator performs the inventory by interviewing a caregiver familiar with the behavior of the patient. A subset of 19 items, including ratings of the patient's ability to eat, dress, bathe, telephone, travel, shop, and perform other household chores has been validated for the assessment of patients with moderate to severe dementia. This is the modified ADCS-ADL, which has a scoring range of 0 to 54, with the lower scores indicating greater functional impairment.

The ability of Namenda 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,

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praxis, and social interaction. The SIB scoring range is from 0 to 100, with lower scores indicating greater cognitive impairment.

Study 1 (Twenty-Eight-Week Study)

In a study of 28 weeks duration, 252 patients with moderate to severe probable Alzheimer's disease (diagnosed by DSM-IV and NINCDS-ADRDA criteria, with Mini-Mental State Examination scores <3 and <14 and Global Deterioration Scale Stages 5-6) were randomized to Namenda or placebo. For patients randomized to Namenda, 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 Namenda-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), Namenda treatment was statistically significantly superior to placebo.

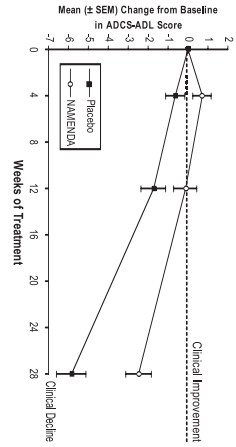


Figure 1: Time course of the change from baseline in ADCS-ADL score for patients completing 28 weeks of treatment.

Figure 2 shows the cumulative percentages of patients from each of the treatment groups who had attained the mean change in the ADCS-ADL shown on the X axis.

The curves show that both patients assigned to Namenda and placebo have a wide range of responses and generally show deterioration (a negative change in ADCS-ADL compared to baseline), but that the Namenda 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.)

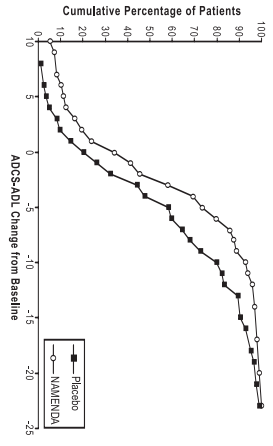


Figure 2: Cumulative percentage of patients completing 28 weeks of double-blind treatment with specified changes from baseline in ADCS-ADL scores.

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 Namenda-treated patients compared to the patients on placebo was 5.7 units. Using an LOCF analysis, Namenda treatment was statistically significantly superior to placebo.

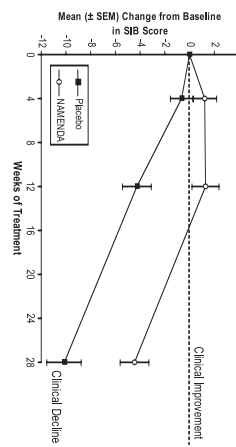


Figure 3: Time course for the change from baseline in SIB score for the two treatment groups over the 28 weeks of the study.

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