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Articles


Books


### Websites

*Many of the reports and fact sheets mentioned in this issue are available on the following Websites.*

**The Access Project.** Brandeis University research affiliate and community-based resource center aimed at improving health and healthcare access. [www.accessproject.org](http://www.accessproject.org)

**America’s Health Insurance Plans (AHIP).** National association representing health insurance companies. [www.ahip.org](http://www.ahip.org)

**Cato Institute.** Non-profit research foundation focusing on a broad spectrum of public policy issues. [www.cato.org](http://www.cato.org)

**Commonwealth Fund.** Private research and grant-funding organization aimed at improving healthcare practice and policy in the U.S. and other industrialized countries. [www.commonwealthfund.org](http://www.commonwealthfund.org)

**Employee Benefit Research Institute.** Non-partisan organization providing research, data analysis, and public education on national policies related to employee benefits. [www.ebri.org](http://www.ebri.org)

**Galen Institute.** Non-profit research organization focusing on healthcare policy. [www.galen.org](http://www.galen.org)

**HSA Consulting Services, LLC.** Healthcare consulting practice specializing in HSAs and consumer-driven healthcare issues. [www.hsaed.com](http://www.hsaed.com)

**Kaiser Family Foundation.** Non-profit private foundation providing research and policy analysis, news, and information on major healthcare issues. [www.kff.org](http://www.kff.org)

**United States Department of the Treasury.** Federal agency with detailed information about tax-advantaged benefits programs such as HSAs and HRAs. [www.treasury.gov](http://www.treasury.gov)
Namenda (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer’s type.

**CONTRAINDICATIONS**

Namenda (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

**PRECAUTIONS**

*Information for Patients and Caregivers:*

Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose adjustments in the event of significant changes in body weight. In the food-drug interaction study, Namenda (5 and 10 mg) did not affect the bioavailability of the antihypertensive drug felodipine, an oral dihydropyridine calcium channel blocker. However, in a dose-related study, Namenda (5 mg) decreased the bioavailability of felodipine by about 80% under alkaline urine conditions at pH 8. Therefore, alterations in urine pH towards the alkaline condition may lead to an accumulation of memantine resulting in increased plasma levels of memantine.

**Special Populations**

**Hepatic Impairment**

Namenda undergoes partial hepatic metabolism, with about 48% of administered dose excreted in urine as unchanged drug or as the sum of parent drug and the N-glucuronide conjugate (74%). No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Namenda should be administered with caution to patients with severe hepatic impairment.

**Renal Impairment**

No dosage adjustment is needed in patients with mild or moderate renal impairment. A dosage reduction is recommended in patients with severe renal impairment (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in Full Prescribing Information).

**Drug-Drug Interactions**

*N-methyl-D-aspartate (NMDA) antagonists:* The combined use of Namenda with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

**Effects of Namenda on substrates of microsomal enzymes:** In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2; -264; -292; -296; -297, -344) showed minimal inhibition of these enzymes by memantine. In addition, in vitro studies indicate that at concentrations exceeding those anticipated in vivo, memantine does not induce the cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2E1, and CYP3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

**Effects of inhibitors and/or substrates of microsomal enzymes on Namenda:** Memantine is predominantly renally eliminated, and drugs that are substrates or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

**Acetylcholinesterase (AChE) inhibitors:** Coadministration of Namenda with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. 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 and donepezil was similar to that of donepezil alone.

**Drugs eliminated via renal mechanisms:** Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic secretory system, including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cinmetidine, ranitidine, quindine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of Namenda 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 with the 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®.

**Drugs that make the urine alkaline:** The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by drugs that make the urine alkaline: the clearance of memantine resulting in increased plasma levels of memantine.

**Carcinogenesis, Mutagenesis and 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 for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m² basis, respectively) through 128 weeks. Namenda produced no evidence of genotoxic potential when evaluated in an 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.

**Pregnancy**

Pregnancy Category B: Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 10 times, respectively, the maximum recommended human dose [MRHD] on a mg/m² basis).

Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the post-partum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m² basis.

There are no adequate and well-controlled studies of memantine in pregnant women. Memantine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

It is not known whether memantine is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother.

**Pediatric Use**

There are no adequate and well-controlled trials documenting the safety and efficacy of memantine in any illness occurring in children.

**ADVERSE REACTIONS**

The experience described in this section derives from studies in patients with Alzheimer’s disease and vascular dementia.

**Adverse Events Leading to Discontinuation:** In placebo-controlled trials in which dementia patients received doses of Namenda up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the Namenda group as in the placebo group. No individual adverse event was associated with the discontinuation of treatment in 1% or more of Namenda-treated patients and at a rate greater than placebo.

**Adverse Events Reported in Controlled Trials:** The reported adverse events in Namenda (memantine hydrochloride) trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ. Table 1 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients treated with Namenda compared to patients treated with placebo. No adverse event occurred at a frequency of at least 5% and twice the placebo rate.

**Table 1: Adverse Events Reported in at Least 2% of Patients Receiving Namenda and at a Higher Frequency than Placebo-Treated Patients**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Event</th>
<th>Placebo (N = 922)</th>
<th>Namenda (N = 940)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Central and Peripheral Nervous System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hallucination</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughing</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Other adverse events occurring with an incidence of at least 2% in Namenda-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, abdominal pain, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.

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

Vital Sign Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in 4 variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Namenda treatment.

ECG Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in the variables. These analyses revealed no clinically important changes in ECG parameters associated with Namenda treatment.

Other Adverse Events Observed During Clinical Trials
Namenda has been administered to approximately 1350 patients with dementia, of whom more than 1200 received the maximum recommended dose of 50 mg/day. Patients received Namenda treatment for periods of up to 884 days, with 862 patients receiving 24 weeks of treatment and 387 patients receiving 48 weeks or more of treatment. Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 4 open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using WHO terminology, and event frequencies were calculated across all studies. All adverse events occurring in at least two patients are included, except for those already listed in Table 1. WHO terms too general to be informative, minor symptoms or events unlikely to be drug-caused, e.g., because they are common symptoms of dementia.

Body as a Whole: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various laboratory chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in the variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Namenda treatment.

Frequent:

- somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting,
- sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, choreoathetosis, to several degrees, delirium, transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia.

- urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, abdominal pain, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.

- nominally related to Namenda treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

- increases in mean standing vital sign measures for Namenda and placebo in elderly normal patients meeting criteria for potentially clinically significant changes from baseline in the variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Namenda treatment.

- 1/100 to 1/1000 patients. These adverse events are not necessarily related to Namenda treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

- signs and symptoms associated with memantine overdose in clinical trials and from worldwide marketing experience include agitation, confusion, ECG changes, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of memantine worldwide was 2.0 grams in a patient who took memantine in conjunct with unspecified antiobiotic medications. The patient experienced coma, diplopia, and agitation, but recovered fully without sequelae.

- Events Reported Subsequent to the Marketing of Namenda, both US and Ex-US
Although no causal relationship to memantine treatment has been found, the following adverse events have been reported to be temporarily associated with memantine treatment and are not described elsewhere in labeling: aspiration pneumonia, asthenia, atrioventricular block, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, cholelithiasis, claudication, colitis, deep venous thrombosis, depressed level of consciousness (including loss of consciousness and rare reports of coma), dyskinesia, dysphagia, encephalopathy, gastritis, gastrointestinal reflux, grand mal convulsions, intracranial hemorrhage, hepatitis (including increased ALT and AST hepatic failure), hyperglycemia, hyperlipidemia, hypoglycemia, ileus, increased INR, impotence, lightheadedness, malaise, myoclonus, neuroleptic malignant syndrome, acute pancreatitis, Parkinsonism, acute renal failure (including increased creatinine and renal insufficiency), prolonged QT interval, restlessness, sepsis, Stevens-Johnson syndrome, suicidal ideation, sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, choreoathetosis, to several degrees.

- First: syncope, Infrequent: hypothermia, allergic reaction.

- Cardiovascular System: First: cardiac failure, Infrequent: angina pectoris, bradycardia, myocardial infarction, thrombophlebitis, atrial fibrillation, hypotension, cardiac arrest, postural hypotension, pulmonary embolism, pulmonary edema.


- Metabolic and Nutritional Disorders: First: increased alkaline phosphatase, decreased weight. Infrequent: dehydration, hypokalemia, aggravated diabetes mellitus.

- Psychiatric Disorders: First: aggressive reaction. Infrequent: delusion, personality disorder, emotional lability, nervousness, sleep disorder, libido increased, psychosis, amnesia, apathy, paranoid reaction, thinking abnormal, crying abnormal, appetite increased, paroniria, delirium, depersonalization, nervousness, suicide attempt.


- Special Senses: First: cataract, conjunctivitis. Infrequent: macular lutea degeneration, decreased visual acuity, decreased hearing, tinnitus, blepharitis, blurred vision, corneal opacity, glaucoma, conjunctival hemorrhage, eye pain, retinal hemorrhage, xerophthalmia, diplopia, abnormal lacrimation, myopia, retinal detachment.


- Events Reported Subsequent to the Marketing of Namenda, both US and Ex-US
Although no causal relationship to memantine treatment has been found, the following adverse events have been reported to be temporarily associated with memantine treatment and are not described elsewhere in labeling: aspiration pneumonia, asthenia, atrioventricular block, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, cholelithiasis, claudication, colitis, deep venous thrombosis, depressed level of consciousness (including loss of consciousness and rare reports of coma), dyskinesia, dysphagia, encephalopathy, gastritis, gastrointestinal reflux, grand mal convulsions, intracranial hemorrhage, hepatitis (including increased ALT and AST hepatic failure), hyperglycemia, hyperlipidemia, hypoglycemia, ileus, increased INR, impotence, lightheadedness, malaise, myoclonus, neuroleptic malignant syndrome, acute pancreatitis, Parkinsonism, acute renal failure (including increased creatinine and renal insufficiency), prolonged QT interval, restlessness, sepsis, Stevens-Johnson syndrome, suicidal ideation, sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, choreoathetosis, to several degrees.
Improves function, delays onset of behavioral symptoms, and provides benefits in cognition.  
Excellent safety and tolerability with low risk of unpleasant gastrointestinal side effects.  
Significantly reduces monthly caregiving time.  
Proven effective first-line and in combination with an acetylcholinesterase inhibitor.

Preferred status on the majority of health plan and Medicare Part D formularies.  
NAMENDA® (memantine HCl) is indicated for the treatment of moderate to severe Alzheimer’s disease.  
NAMENDA is contraindicated in patients with known hypersensitivity to memantine HCl or any excipients used in the formulation. The most common adverse events reported with NAMENDA vs placebo (≥5% and higher than placebo) were dizziness, confusion, headache, and constipation. In patients with severe renal impairment, the dosage should be reduced.


For more details, please visit www.namenda.com. Please see brief summary of Prescribing Information on the adjacent pages.