For More Information

Articles
An updated survey of health care claims receipt and processing times. AHIP Center for Policy and Research. May 2006. www.ahip.org


Kilo CM, Endsley S. As good as it could get: remaking the medical practice. Family Practice Management. May 2000.


Books


Daigrepont J, Mink L. *Starting a Medical Practice*. Chicago, IL: AMA; 2003.


**Organizations**

Medical Group Management Association. [www.mgma.com](http://www.mgma.com)

The National Medical Foundation for Tax Planning and Asset Protection, (800) 375-2453

Professional Association of Healthcare Office Management. [www.pahcom.com](http://www.pahcom.com)
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 reduction interval of one week between dose increases.

Neurological Conditions
Seizures: Namenda has not been systematically evaluated in patients with a seizure disorder. In clinical trials of Namenda, seizures occurred in 0.2% of patients treated with Namenda and 0.5% of patients treated with placebo.

Genitourinary Conditions
Conditions that raise urine pH may decrease the urinary elimination 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 combination 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, -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, CYP2C9, CYP2P1, 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 and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

Acetylcholinesterase (AChE) inhibitors: Co-administration of Namenda with the AChE inhibitor donepezil HCI 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, co-administration of drugs that use the same renal tubular mechanism, including hydrochlorothiazide (HCTZ), tramterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, co-administration 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, co-administration of memantine with the antihypertensive drug Guvaclovine® (glyburide and metformin HCI) did not affect the pharmacokinetics of memantine, metformin and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Guvaclovine®.

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 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.

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 (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 vivo 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 (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.

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 20 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 in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with Namenda than for those 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 Controlled Clinical Trials 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>Fatigue</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>Pain</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>Hypertension</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Central and Peripheral Nervous System</td>
<td>Dizziness</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td>Headache</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td>Constipation</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td>Vomiting</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal System</td>
<td>Back pain</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Confusion</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Somnolence</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Hallucination</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>Coughing</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>Dyspnea</td>
<td>2</td>
<td>3</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, abnormal gait, 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 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 to endpoint. These analyses were performed using laboratory values recorded at baseline and at each visit. The changes in vital signs in patients treated with Namenda. A comparison of supine and standing vital sign measures for Namenda and placebo in elderly normal subjects indicated that Namenda treatment is not associated with orthostatic changes.

Laboratory Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various serum 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 were performed using laboratory test parameters associated with Namenda treatment.

EGC 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 these 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 20 mg/day. Patients received Namenda treatment for periods of up to 884 days, with 862 patients receiving at least 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 expansion trials were recorded as adverse events if these events were not different clinically important changes in laboratory test parameters associated with Namenda treatment.

Physical and Psychological Dependence:

Although no causal relationship to memantine treatment has been found, the following adverse events have been reported to be temporally associated with memantine treatment and are not described elsewhere in labeling: insomnia, urinary incontinence, increased appetite, restlessness, suicidal ideation, and from worldwide marketing experience include agitation, confusion, ECG changes, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, tetany, tremor, weakness. The largest known ingestion of memantine worldwide was 2.0 grams in a patient who took memantine in conjunction with unspecified antidepressant medications. The patient experienced coma, delirium, and from the marketing of Namenda, both US and Ex-US

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Treat today with NAMENDA
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- Proven effective first-line and in combination with an acetylcholinesterase inhibitor

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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.

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