

CLINICAL CAPSULES

Obesity-Related Mortality

Obesity was associated with an estimated 111,909 excess deaths in the United States in the year 2000, reported Katherine M. Flegal, Ph.D., of the National Center for Health Statistics, Hyattsville, Md., and her associates.

A study by the Centers for Disease Control and Prevention published last year in the Journal of the American Medical Association erroneously reported that obesity-related deaths reached 400,000 per year between 1990 and 2000.

Dr. Flegal and her associates estimated

relative risks of mortality using National Health and Nutrition Examination Survey (NHANES) data (JAMA 2005;293:1861-7).

Most of the excess deaths (82,066) occurred in people with a body mass index (BMI) of at least 35 kg/m², compared with normal-weight people. Among overweight people, the estimated number of deaths was 86,094 fewer than among normal-weight people. When mortality was calculated for overweight people combined with obese people, the estimated number of excess deaths was 25,814, compared with people of normal weight.

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 postpartum 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.

Body System Adverse Event	Placebo (N = 922) %	Namenda (N = 940) %
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucination	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

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 in these variables. There were no clinically important 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 these 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 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

Predicting Postmenopausal CV Risk

Screening for an enlarged waist in combination with elevated triglycerides appears to be a simple, effective tool to flag postmenopausal women at increased risk for accelerated atherogenesis and related adverse outcomes, reported Laszlo B. Tanko, M.D., and his associates at the Center for Clinical and Basic Research, Ballerup, Denmark.

In a study of 557 Copenhagen-area women aged 48-76 years followed for an average of 8.5 years, 16% of the women had enlarged waist (at least 88 cm) with elevated triglyceride levels (EWET), and 18% had metabolic syndrome, defined as

having at least three of five criteria: enlarged waist, elevated triglycerides, elevated blood pressure, low HDL cholesterol, and impaired fasting glucose (Circulation 2005;111:1883-90).

EWET was linked to a nearly fivefold increased risk for fatal cardiovascular events, while metabolic syndrome was linked to a more than threefold increased risk. Excluding women with diabetes at baseline did not change the pattern. EWET also was better than metabolic syndrome for predicting annual progression of aortic calcification, Dr. Tanko and his associates said.

Middle-Aged Obesity and Dementia

People who are obese or overweight at middle age are at significantly greater risk for dementia in later life than normal-weight people, reported Rachel A. Whitmer, Ph.D., of the division of research, Kaiser Permanente, Oakland, Calif.

The investigators prospectively followed 10,276 people enrolled in the Kaiser Permanente medical program of northern California who were 40-45 years old between 1964 and 1973. At midlife, 10% were obese (BMI of 30 kg/m² or greater), 36% overweight (BMI 25-29.9 kg/m²), and 53% normal weight (BMI 18.6-24.9 kg/m²).

From January 1994 to April 2003, people who were obese at midlife had a 74% greater risk of dementia, compared with people who had been of normal weight, while overweight people had a 35% greater risk.

In women, the corresponding increases were 107% for obesity and 55% for overweight; no significant differences were found in men.

People in the highest quintile of subscapular skinfold at midlife had a 72% increased risk of dementia, while people in the highest quintile of triceps skinfold had a 59% increased risk of dementia, compared with people in the lowest fifth of the two measures, Dr. Whitmer reported in the April 29 online edition of the British Medical Journal.

Obesity Rising for All Income Levels

Obesity has largely been considered a problem for people with lower income levels, but new data suggest that the waistlines of people with higher income levels are catching up, reported Nidhi Maheshwari, M.B., of the University of Iowa College of Public Health, Iowa City.

For Americans making more than \$60,000 a year (adjusted to 2000 dollars), the prevalence of obesity was 9.7% in 1971-1974 and rose significantly to 26.8% in 2001-2002, based on data on people 20 years old or older who were interviewed for NHANES between 1971 and 2002, according to the study, presented at a conference on cardiovascular disease epidemiology and prevention sponsored by the American Heart Association.

The prevalence of obesity among Americans making less than \$25,000 a year was 22.5% in 1971-1974 and 32.5% in 2001-2002. Among Americans making \$25,000 to \$39,999 a year, the prevalence was 16.1% in 1971-1974 and 31.3% in 2001-2002. The prevalence among those making \$40,000-\$60,000 a year was 14.5% in 1971-1974 and 30.3% in 2001-2002.

—Kevin Foley



Rx Only

Brief Summary of Prescribing Information.

For complete details, please see full Prescribing Information for Namenda.

INDICATIONS AND USAGE

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 escalation (minimum 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, but the major fraction of a dose (57-82%) is excreted unchanged in urine. The pharmacokinetics of memantine in patients with hepatic impairment have not been investigated, but would be expected to be only modestly affected.

Renal Impairment

There are inadequate data available in patients with mild, moderate, and severe renal impairment but it is likely that patients with moderate renal impairment will have higher exposure than normal subjects. Dose reduction in these patients should be considered. The use of Namenda in patients with severe renal impairment is not recommended.

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, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. 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: 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 system, including hydrochlorothiazide (HCTZ), triamterene (TA), cimetidine, ranitidine, quinidine, 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%.

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 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.

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 30 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 postpartum period. Slight maternal

Forest Pharmaceuticals, Inc.
Pharmaceuticals • Therapeutics • Healthcare • Ethical • Managed Care • Specialty Sales

Licensed from Merz Pharmaceuticals GmbH

Rev. 05/05

© 2005 Forest Laboratories, Inc.