

# EDs Bring Profits, Not Just Patients, to Hospitals

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SAN FRANCISCO — Patients admitted to the hospital through the emergency department generated significant profit and produced double the relative profitability of patients admitted directly to the hospital, Brian J. Browne, M.D., reported at the annual meeting of the American College of Emergency Physicians.

The results of his retrospective analysis

debunk the image of the emergency department (ED) as a “cost center” or “loss leader”—in other words, a necessary expense supported by the rest of the hospital’s clinical services, said Dr. Browne, chief of emergency medicine at the University of Maryland, Baltimore, and director of emergency medical services at the University of Maryland Medical Center.

The findings should be useful to ED administrators when they need to lobby for institutional support, he said.

The investigators defined the direct margin as the amount by which net revenue exceeded the sum of direct fixed and variable components. Out of the margin, the hospital pays overhead expenses, and what remains is profit. Net profit was the amount by which net revenue exceeded the sum of all costs, both direct and indirect.

In the study of 89,757 discharges during July 2000-June 2003, patients admitted to the ED generated 19% of the hospital revenue, 20% of the direct margin, and 33%

of profits from all hospital admissions, said Dr. Browne and coinvestigator, Dick Kuo, M.D., also of the medical center.

Patients who were admitted directly to the hospital produced higher totals for net revenue, costs, direct margin, and profit because more patients entered the hospital directly rather than through the ED—73% vs. 27%, respectively. However, it’s notable that patients admitted through the ED generated profit—totaling a third

## Namenda memantine HCl

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 nicotinic, 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 60% 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/m<sup>2</sup> 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/m<sup>2</sup> 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 vitro* cytogenetic 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/m<sup>2</sup> 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/m<sup>2</sup> basis).

Slight maternal toxicity, decreased pup weights and an increased incidence of nonossified 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

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/m<sup>2</sup> 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 children with dementia of the Alzheimer’s type.

#### 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) %
<b>Body as a Whole</b>		
Fatigue	1	2
Pain	1	3
<b>Cardiovascular System</b>		
Hypertension	2	4
<b>Central and Peripheral Nervous System</b>		
Dizziness	5	7
Headache	3	6
<b>Gastrointestinal System</b>		
Constipation	3	5
Vomiting	2	3
<b>Musculoskeletal System</b>		
Back pain	2	3
<b>Psychiatric Disorders</b>		
Confusion	5	6
Somnolence	2	3
Hallucination	2	3
<b>Respiratory System</b>		
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, gait abnormal, 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

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 in the study population. Events are classified by body system and listed using the following definitions: frequent adverse events—those occurring in at least 1/100 patients; infrequent adverse events—those occurring in 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.

**Body as a Whole:** Frequent: syncope. Infrequent: hypothermia, allergic reaction.

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

**Central and Peripheral Nervous System:** Frequent: transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia. Infrequent: paresthesia, convulsions, extrapyramidal disorder, hypertonia, tremor, aphasia, hypoesthesia, abnormal coordination, hemiplegia, hyperkinesia, involuntary muscle contractions, stupor, cerebral hemorrhage, neuralgia, ptosis, neuropathy.

**Gastrointestinal System:** Infrequent: gastroenteritis, diverticulitis, gastrointestinal hemorrhage, melena, esophageal ulceration.

**Hemic and Lymphatic Disorders:** Frequent: anemia. Infrequent: leukopenia.

**Metabolic and Nutritional Disorders:** Frequent: increased alkaline phosphatase, decreased weight. Infrequent: dehydration, hyponatremia, aggravated diabetes mellitus.

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

**Respiratory System:** Frequent: pneumonia. Infrequent: apnea, asthma, hemoptysis.

**Skin and Appendages:** Frequent: rash. Infrequent: skin ulceration, pruritus, cellulitis, eczema, dermatitis, erythematous rash, alopecia, urticaria.

**Special Senses:** Frequent: cataract, conjunctivitis. Infrequent: macula 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.

**Urinary System:** Frequent: frequent micturition. Infrequent: dysuria, hematuria, urinary retention.

#### ADVERSE EVENTS FROM OTHER SOURCES

Memantine has been commercially available outside the United States since 1992, and has been evaluated in clinical trials including trials in patients with neurodegenerative Parkinson’s disease, brain stroke, and spasticity. The following adverse events of possible importance for which there is inadequate data to determine the causal relationship have been reported to be temporally associated with memantine treatment in more than one patient and are not described elsewhere in labeling: acne, bone fracture, carpal tunnel syndrome, dacryodact, hyperkalemia, impotence, otitis media, thrombocytopenia.

#### ANIMAL TOXICOLOGY

Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers II 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 on a mg/m<sup>2</sup> basis. The potential for induction of central neuronal vacuolation and necrosis by NMDA receptor antagonists in humans is unknown.

#### DRUG ABUSE AND DEPENDENCE

**Controlled Substance Class:** Memantine HCl is not a controlled substance. **Physical and Psychological Dependence:** Memantine HCl is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

#### OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine. In a documented case of an overdose with up to 400 mg of memantine, the patient experienced restlessness, psychosis, visual hallucinations, somnolence, stupor and loss of consciousness. The patient recovered without permanent sequelae.

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DR. BROWNE

of all profits—despite inclusion of ED costs, Dr. Browne said.

Patients admitted directly to the hospital generated about 81% of revenues, 80% of the direct margin, and 67% of total profits. (Percentages may not add up because of rounding.)

The ED patient group, however, had a higher direct margin (expressed as a percentage of net revenue), compared with the direct-admission group—40% vs. 37%. And ED admissions were twice as efficient when comparing profit as a percent of the revenue—10% vs. 5% in the direct-admission group, Dr. Browne said.

The analysis looked at direct and indirect costs. Data for the ED patient group included all costs generated both in the ED and in the hospital for patients admitted through the ED. The analysis included only revenues actually collected, not charges that were never collected. “Many previous papers looked at charges, which is not real,” Dr. Browne said.

The direct-admission group included both elective admissions and transfers into the hospital that did not go through the ED, including 21,223 admissions to the trauma center.

The Case Mix Index and average length of stay were comparable between groups. The Case Mix Index is a measure of case severity (complexity and acuity), so the ED patients were slightly less severe cases than direct-admit patients. The Case Mix Index was 1.10 in the ED group and 1.28 in the direct-admit group. The length of stay after admission (not including time in the ED) averaged 5.8 days in the ED group and 6 days in the direct-admit group.

Under traditional cost accounting practices, the ED is seen only as a source of admissions, with associated costs. “That model is unfair, and doesn’t recognize the full impact of the ED and those patients for the finances of the hospital accurately,” Dr. Browne said.

Hopefully, the data will help change the traditional view of the ED, Dr. Browne said, so that “when I ask for something for the common good of the ED—like an information system update, or ultrasound equipment, or a lab—the administration should recognize that the ED is a major player in profitability.”