

# Facts: about memantine

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This fact sheet has been reviewed by the Alzheimer's Association Clinical Issues and Interventions Work Group. It is provided for your information only and does not represent an endorsement of memantine by the Alzheimer's Association. Updated January 13, 2004.

## **What is memantine?**

Memantine is a drug approved in October 2003 by the U.S. Food and Drug Administration (FDA) for treatment of moderate to severe Alzheimer's disease. Forest Laboratories Inc., memantine's U.S. developer, will market the drug under the trade name Namenda<sup>®</sup>. Memantine was first approved in Germany for treatment of various neurological disorders in 1982, where it is marketed by Merz + Co. as Axura<sup>®</sup>. Since 2002, it has been approved in the rest of the European Union, where it is marketed by Lundbeck as Ebixa<sup>®</sup>.

Forest announced availability of memantine in U.S. pharmacies in January 2004.

## **What kind of drug is memantine?**

Memantine is classified as an uncompetitive low-to-moderate affinity N-methyl-D-aspartate (NMDA) receptor antagonist, the first Alzheimer drug of this type approved in the United States. It appears to work by regulating the activity of glutamate, one of the brain's specialized messenger chemicals involved in information processing, storage, and retrieval. Glutamate plays an essential role in learning and memory by triggering NMDA receptors to allow a controlled amount of calcium to flow into a nerve cell, creating the chemical environment required for information storage.

Excess glutamate, on the other hand, overstimulates NMDA receptors to allow too much calcium into nerve cells, leading to disruption and death of cells. Memantine may protect cells against excess glutamate by partially blocking NMDA receptors.

Memantine's action differs from the mechanism of the cholinesterase inhibitors that were previously approved in the United States for treatment of Alzheimer symptoms. Cholinesterase inhibitors temporarily boost levels of acetylcholine, another messenger chemical that becomes deficient in the Alzheimer brain.

## **What is the evidence that memantine may help Alzheimer symptoms?**

Forest submitted evidence in support of memantine's effectiveness in treating moderate to severe Alzheimer's disease in a new drug application to the FDA in December 2002, amended in January 2003. In September 2003, the FDA's Peripheral and Central Nervous System Drug Advisory Committee met to respond to specific questions raised by the FDA regarding application data. Briefing documents and summaries of advisory committee critiques are available on the FDA Web site at

<http://www.fda.gov/ohrms/dockets/ac/cder03.html#PeripheralandCentralNervousSystemDrugs>. At the conclusion of its meeting, the advisory committee voted unanimously that the following data submitted in the new drug application support the safety and effectiveness of memantine in treating moderate to severe Alzheimer's disease:

- (1) **A 28-week U.S. study enrolling 252 individuals with moderate to severe Alzheimer's disease and initial scores ranging from 3 – 14 on the Mini-Mental State Examination (MMSE).** In this double-blind study, participants were randomly assigned to receive either 10 mg of memantine twice a day or a placebo. Those receiving memantine showed a small but statistically significant benefit in a test of their ability to perform daily activities and on the Severe Impairment Battery, a test designed to measure cognition in profoundly incapacitated individuals. On the Clinician Interview-Based Impression of Change Plus Caregiver Input, a measure of overall function, memantine recipients also showed a benefit that was significant in one analysis but not in another. In this study, when participants with MMSE scores of less than 10 were considered as a separate group, memantine recipients showed no benefit compared to those who received placebo on either daily activities or overall function.
- (2) **A 24-week U.S. study enrolling 404 individuals with moderate to severe Alzheimer's disease and initial MMSE scores from 5 – 14 who had been taking donepezil (Aricept®) for at least six months, with a stable dose for at least three months.** In this double-blind study, participants were randomly assigned to receive either 10 mg of memantine twice a day or a placebo in addition to their donepezil. Those receiving memantine showed a statistically significant benefit in performing daily activities and on the Severe Impairment Battery, while participants taking donepezil plus placebo continued to decline.

Some advisory committee members considered memantine's effect modest, similar in scope to the effect seen with cholinesterase inhibitors.

The advisory committee found problems with the design of a third submitted study, conducted in Latvia, because it enrolled individuals with vascular dementia as well as Alzheimer's disease. An additional issue was that although the data showed a positive effect for memantine on reducing dependence on care, the study lacked an acceptable measure of effect on cognitive function. According to current FDA standards, drugs approved specifically to treat Alzheimer's disease must show a benefit on cognitive symptoms as well as on overall function, which confirms that the effect on cognition is clinically meaningful.

In June 2003, Forest reported preliminary results from another add-on therapy trial enrolling participants with mild to moderate Alzheimer's who were also taking any of three commonly prescribed cholinesterase inhibitors—donepezil (Aricept®), galantamine (Reminyl®), or rivastigmine (Exelon®). Data from this trial were not included in the new drug application seeking approval of memantine for moderate to severe disease. According to the company, the data showed that participants receiving memantine in combination with a cholinesterase inhibitor did not experience significantly greater

benefit in cognition or overall function than those who received a cholinesterase inhibitor and a placebo. These preliminary results suggest that memantine may not be as effective in individuals with mild to moderate Alzheimer's who are taking a cholinesterase inhibitor as it may in more severely ill individuals. This data has not yet been peer reviewed or presented in a professional forum.

### **How is memantine supplied and prescribed?**

Memantine is supplied as an oral medication in 10 mg tablets. Forest is providing prescribing information at [www.namenda.com](http://www.namenda.com) or by calling 1.877.2-NAMENDA (1.877.262.6363). Adverse effects occurring more commonly with memantine than with placebo included headache, constipation, confusion, and dizziness.

### **Where can I get more information?**

The Alzheimer's Association will update this fact sheet as more information becomes available from recent clinical trials or from postmarketing experience with memantine. The latest version of this fact sheet is always available on our Web site at [www.alz.org](http://www.alz.org) or by calling our 24/7 Contact Center at 800.272.3900. You may also call Forest directly at 800.678.1605 and ask for the Professional Affairs Division.