Facts : About Memantine, an experimental Alzheimer drug

What is memantine?

Memantine is a drug developed by the German company Merz + Co. for treatment of symptoms of dementia. The drug has been approved in Germany for more than 10 years, where it is marketed by Merz under the trade name Axura®. In May 2002, the European Union's Committee for Proprietary Medicinal Products approved mementine for treatment of moderately severe to sever Alzheimer's throughout the European Union, where it is marketed by Lundbeck as Ebixa®.

Memantine appears to regulate the activity of glutamate, one of the brain's specialized messenger chemicals that affects the activity of several different types of receptors (cell- surface "docking sites"), including AMPA and NMDA receptors. At normal concentrations, glutamate plays an essential role in learning and memory by attaching to AMPA receptors. This attachment triggers NMDA receptors to allow a certain amount of calcium to flow into a cell.

Subnormal glutamate levels may interfere with learning and memory by leading to insufficient AMPA receptor activity. Excess glutamate, on the other hand, over stimulates AMPA receptors, which in turn leads NMDA receptors to allow excess calcium to flow into cells. Excess calcium causes cell disruption and cell death. Alzheimer's disease may involve both excesses and deficiencies of glutamate at different times and under different circumstances.

Memantime may protect against excess glutamate by blocking NMDA receptors, preventing calcium from flowing into cells. It also may increase the activity of AMPA receptors when glutamate levels are low, supporting learning and memory.Memantine's action in the glutamate system differs from the activity of the cholinesterase inhibitors that are currently approved in the United States for treatment of Alzheimer's.

Cholinesterase inhibitors temporarily boost levels of acetylchline, another messenger chemical that becomes deficient in the Alzheimer brain. These differing modes of action raise the possibility that individuals may be ale to take memantine either as stand-alone therapy or in combination with cholinesterase inhibitors.

Where is memantine in the drug development process?

Memantine is now under development by Forest Laboratories, Inc., for marketing in the United States. Three recent trials of memantine have already been completed – one in Latvia, one U.S. Phase III trial testing memantine as a stand-alone treatment and another Phase III trial testing memantine in combination with denepezil (Aricept®), a cholinesterase inhibitor marketed by Eisai, Inc., and Pfizer Inc. In the sing-therapy trial, participants with moderate to severe Alzheimer's who received 10 milligrams of memantine twice a day during the six months of the study showed

significantly less decline in thinking skills and ability to perform daily self-care activities than enrollees who received a placebo (a similar but inactive treatment).

Data from the combination therapy trial, which enrolled more than 400 participants with moderate to severe Alzheimer's disease at 37 U.S. study centers, suggest that individuals who received both memantine and donepezil fared better in terms of their thinking skills and ability to perform daily activities than those who took donepezil and a placebo.

These results have been presented to a professional psychopharmacology conference and at the April 2003 meeting of the American Academy of Neurology, but still need to undergo peer review and be published in a scientific journal before they attain the stature of the stand-alone studies. In June 2003, Forest reported preliminary results from another combination 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®).

According to the company, participants receiving memantine in combination with a cholinesterase inhibitor did not experience any 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 mild to moderate Alzheimer's as was previously demonstrated in more severely ill individuals. This data has not been peer reviewed or presented in a professional forum.

Two additional nationwide Phase III trials of treatment with memantine alone remain on going, one involving individuals with mild to moderate Alzheimer's and one enrolling participants in moderate to severe stages. In December 2002, Forest submitted its new drug application (NDA) to the U.S. Food and Drug Administration (FDA). The NDA, which is the formal request for approval in treating moderate to severe Alzheimer's disease, presents for the FDA's review all of the company's data gathered so far during the drug development process.

According to Forest, the FDA "accepted the NDA for filing" on January 30, 2003. The FDA now has 10 months from January 20 to approve memantine or issue a letter finding the drug "not approvable" or "approvable". A "not approvable" letter details defects in the data or the submission that are too serious to fix. An "approvable" determination finds that the drug can ultimately be approved, pending corrections to the submission.