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Quick Pulse

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FOREST LABORATORIES' MEMANTINE

To check on the outlook for Forest Lab's memantine, a senior FDA official several clinical psychiatrists, and five Alzheimer's Disease researchers were interviewed. **These comments may be useful in assessing the impact of the recent failure of a trial of memantine plus Aricept in mild-moderate Alzheimer's.**

Memantine, a moderate-affinity NMDA (N-methyl-D-aspartate) receptor antagonist, has been in development in the U.S. for several years. By July 2000, Merz had received approval to sell it in Germany, and memantine has since gained approval in other European countries but not the U.S. Forest has the U.S. marketing rights.

Memantine has been in Phase III trials in the U.S. since at least 2000. A Phase III trial was reported in 2000 on 250 moderate-to-severe Alzheimer's patients at 32 centers in the U.S., demonstrating a beneficial effect. The most common side effects were dizziness (but no increase in falls compared to placebo), headache and fatigue, all of which were under 10%. The dropout rate was less than placebo. A Merz official said, "The trial found a 10% delay in the time necessary for caregiving per month and a drop in the rate of institutionalization. Patients were permitted to take concomitant neurepileptics but not anti-psychotics, and it was hard to convince the investigators to do this, but it turned out that patients also had less agitation on memantine than on placebo." A company official indicated a second Phase III trial would be required for FDA approval, and Forest planned an Alzheimer's prevention trial. The expected dosing was 10 mg BID orally.

Three years later, memantine is still awaiting FDA approval. The PDUFA date is October 19, 2003. Forest expects memantine to require an FDA advisory panel. The next one is scheduled for July 18, 2003, but the agenda for that meeting has not yet been announced, and no later panel meeting dates have been released so far. Even before the failed MEM-MD-12 (combination therapy in mild-moderate Alzheimer's Disease) trial, Forest did **not** expect the FDA to approve memantine by the PDUFA date in October 2003. Rather, the company expected an Action Letter (formerly called an approvable letter) requesting additional information. However, they did not expect the requested information to be substantial, and they did not expect to have to do additional clinical trials. The company estimate was for approval in the first half of 2003, perhaps as late as mid-2004.

In the completed trials in monotherapy (Study 9605, reported in the New England Journal of Medicine in April 2003) and combination therapy (MEM-MD-02, reported at the American Academy of Neurology meeting in Hawaii), there were two primary endpoints: (1) Severe Impairment Battery (SIB) and (2) a measure of functionality (activities of daily living). The secondary endpoint was global efficacy.

Other Alzheimer's drugs have used cognition (measured by ADAS-COG) and global efficacy as endpoints. The Forest official said, "Use of SIB is a potential issue, but it is being recognized more and more…Our main task is to educate people about SIB." The investigator said, "SIB is not a good measure for the mildest patients, but it is good for all other patients…SIB was used in all the trials for European approvals of memantine…Pfizer also used SIB in a study published in 2001…I don't think SIB will be an issue; it is becoming well-recognized." A senior FDA official, asked about the use of SIB, said only, "The primary endpoints in an Alzheimer's drug trial can't both measure the same thing, such as functionality and global efficacy."

In May 2003, Forest reported that a pivotal placebo-controlled study of memantine in the treatment of neuropathic pain in diabetic patients failed to demonstrate a statistically significant difference versus placebo in the trial's primary endpoints.

Three memantine trials have been underway in the U.S. Data from all three of these will be available this year (2003) ***by press release.***

1. MEM-MD-12: combination therapy in mild-moderate Alzheimer's. 24 week trial, 300-400 patients, primary endpoints: ADAS-COG and CIBIC+. This trial was due to finish first, and **the trial's failure was reported on June 19, 2003:** Memantine did not significantly improve awareness and reasoning (cognition) in patients.

2. MEM-MD-10: monotherapy in mild-moderate Alzheimer's. 24-week trial, 300-400 patients, primary endpoints: ADAS-COG and CIBIC+. **The results may be presented at the American College of Neuropsychopharmacology (ACNP) meeting in San Juan, Puerto Rico, December 7-11, 2003.**

3. MEM-MD-01: monotherapy in moderate-severe Alzheimer's. 24-week trial, 300-400 patients, primary endpoints: SIB and ADL. **Complete results may be presented at the American Geriatrics Society meeting in Las Vegas from May 17-21, 2004.**

Memantine is formulated as a tablet. Dosing in these trials is BID and titrated over four weeks: 5 mg for Week One, 10 mg for Week 2, 15 mg for Week 3 and then the maximum 20 mg for Week 4 and beyond. Additional open label trials are and will be conducted to look at different titrations. A Forest official explained, "Earlier, we thought there was better tolerability with BID dosing, but memantine has a long half life, so there is a potential for QD dosing, and we are looking at that in an open label trial. That is something we are considering for the future and which looks promising."

There currently are no ongoing trials of memantine in vascular dementia (VAD). Internally, Forest has been discussing the possibility of trials in mild cognitive impairment (MCI), but senior officials said they want the mild-moderate data before undertaking anything in MCI. A Forest official also admitted that MCI may be a tough indication to prove, "Acetylcholin-esterase inhibitors are being tested in MCI. At the American Academy of Neurology in Hawaii in April 2003, there was an abstract on a six-month Aricept MCI trial. The primary endpoint was not statistically significant, but a key secondary endpoint (ADAS-COG) was statistically significant."

Forest is seeking a label similar to that for Pfizer's Aricept (donepezil) except for more serious disease – simply: "treatment of moderate to severe Alzheimer's Disease." The company expects the data in the clinical trials section of the label to be similar to that for Aricept, Novartis's Exelon (rivastigmine) and Johnson & Johnson's Reminyl (galantamine). This would allow doctors to use memantine as either monotherapy or combination therapy.

Forest would like to position memantine as monotherapy, an official said, "because of the cost of combination therapy." The company believes most psychiatrists and other doctors currently recognize the drug as a monotherapy agent, not as a combination therapy agent. However, they also want to be able to offer this as a combination therapy.

If and when Forest gets FDA approval for a general Alzheimer's indication, it had planned to submit an sNDA based on the data from the mild-moderate studies, seeking a broader indication – mild to severe disease. The status of those plans is now not clear.

Asked at whom memantine sales will be directed, a Forest official said, "For patients already on an Alzheimer's drug, I would add memantine. For newly diagnosed patients, those who can't tolerate a cholinesterase inhibitor or who are not doing well on a cholinesterase inhibitor, I'd prescribe memantine." We need the mild to moderate indication before we recommend patients be switched from another drug or tapered off another drug after memantine is started." The investigator said, "If it were my mother, I would treat her with both (a cholinesterase inhibitor and memantine) for now…If a patient were really not doing well on a cholinesterase inhibitor or had toleration problems, then I might switch the patient to memantine, but the majority of use will be combination therapy."

Psychiatrists indicted there already is strong patient and patient family demand for memantine. Every doctor questioned said he plans to prescribe memantine, generally in combination with another Alzheimer's drug.

Two of the key things Forest is working on pre-launch are:
1. Convincing doctors of the value of the SIB measure.
2. Promoting the monotherapy data. They want this awareness in the mind of doctors, and they feel that so far this is how most doctors think of memantine – as monotherapy – though they admit that experts will prefer combination therapy, at least initially. ♦