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Quick Pulse

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FDA Peripheral and Central Nervous System Drugs Advisory Committee Meeting on Forest Laboratories' Namenda (memantine)

Bethesda, Maryland
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Compared to other advisory committee meetings, the memantine panel was small, relatively uncontroversial and somewhat shorter than usual. The eight voting members were: five neurologists, a statistician, a psychiatrist, and a pharmacist (the consumer advocate). But it was a big win for Forest – the panel voted unanimously in favor of memantine and Forest on every question posed by the FDA.

An Alzheimer's expert offered this analysis of the severe AD market in the U.S.:

- Prevalence – 1 million
- Diagnosed – 600,000
- Treated with an acetylcholinesterase inhibitors (AChEIs) – 300,000

Forest officials repeatedly emphasized the extensive testing and (European) use that has gone on with this agent over the past 23 years. The company also repeatedly reminded the panel of patient demand for memantine. A Forest official said, "We've been getting more than 1,000 calls a month from patients about memantine." An Alzheimer's Disease specialist said, "There is a burgeoning population in need of symptomatic improvement, and families and society demand that these individual not be 'left behind' and expect new therapies to be developed and made available."

An Emory University neurologist, speaking for Forest, offered this explanation for how memantine works: By down regulating the increased glutamatergic activity and persistent activation of NMDA receptors that contribute to the impaired cognition and memory in AD. He also pointed out these facts about memantine:

- The BID dosing is due to toleration. With its long half live (60-80 hours), QD dosing was possible but not well tolerated. Even with BID dosing, up-titration improves tolerability.
- It is excreted almost entirely in urine.
- There are no effects of food, age or gender.
- There are few drug-drug interactions and no interaction with Pfizer's Aricept (donepezil).
- It rapidly crosses the blood-brain barrier.

A University of Southern California psychiatrist, also speaking for Forest, reviewed the scales Forest used to assess patients in the three trials:

- SIB (Severe Impairment Battery)
- ADCS-ADL, a tool developed by NIH's National Institute on Aging for clinical trials.

Studies Submitted by Forest in Support of the Memantine Application

Study	Design	Dose and Duration	ITT patients on drug	Completors (drug v. placebo)	Functional measure	Cognitive measure and p-value of drug vs. placebo	Global Measure and p-value of drug vs. placebo
9403 (Latvia nursing home)	Monotherapy	10 mg QD, 12 weeks	82	N/A	BGP Care-Dependency (p=.010)	BGP-Cog (p=.001)	CGIC (p<.001)
9605 (U.S. AD outpatients)	Monotherapy	1 mg BID, 28 weeks	126	77% vs. 67%	ADCS-ADL (p=.003)	SIB (p=.002)	CIBIC+ (p=.064)
MD-02 (U.S. AD outpatients)	Combo with Aricept	1 mg BID, 24 weeks	198	85% vs. 75%	ADCS-ADL (p=.02)	SIB (p<.001)	CIBIC+ (p=.028)

Before the vote, an FDA official outlined the agency's concerns with the memantine data:

- Was the scale used to measure cognitive function (SIB) valid since (1) it has never been used for drug approval yet and (2) the MMSE measure (the standard exam used to rate patient severity in other studies) was not statistically significant?
- How significant is the failure of memantine to show efficacy on both primary endpoints in one clinical trial (9605)?
- The post-hoc analysis of severe patients in the 9605 Trial failed to show efficacy. Does that call into question the efficacy of the drug overall?
- Can the Latvian study be used to support this application since the cognitive measures were defined retrospectively and there is uncertainty about the diagnosis of the patients in that trial?

FDA Analysis of Memantine Trial 9605 by MMSE

Measure	Placebo vs. memantine MMSE <10	Placebo vs. memantine MMSE ≥10
ADCS-ADL	p=.2643	p=.0080
CIBIC+	p=.5341	p=.0206
SIB	p=.0082	p=.0073

KEY ISSUES WITH MEMANTINE

Clinical benefits

The FDA's Dr. Russell Katz, Director of the FDA's Division of Neuropharmacologic Drug Products, said: "It is not so much what you tell a caregiver if a spouse has an 8 (on the MMSE)...but do we think memantine works in patients with severe AD, as defined by MMSE? That is a discussion that needs to be had today. That is the real issue from a regulatory point of view….We want to be sure whatever is happening makes a 'big' difference in the patient's life – that patients who couldn't balance a checkbook, now can; that patients who couldn't find their way home, now can. Not that they can just press three numbers of their phone number but that they can now dial the whole phone number. Given the treatment effect seen with memantine, what can we say about that? Do patients actually improve on specific tasks?…Typically, we approve drugs because they make the patient better...In other settings we explicitly said they have to do that…But are the findings on these measures) reflecting ease of care of the patient or are the patients themselves actually better?"

A Forest representative gave an answer that the FDA official indicated was acceptable: "It is the caregiver making the analysis of what the patient can do…But it is patient responses that are being translated by the caregiver -- and at the same time making the caregiver's life easier." An AD expert added, "We don't have any drugs that restore function in AD or any other neurologic disease…Asking that may be unrealistic. But we do see increasing competency…If you look at where changes are occurring, it is in the important elements that people who follow patients notice – e.g., grooming, which is very stressful for caregivers…To see some of that ability return or show stability is important."

A public witness offered his family's experience as proof of the clinical benefit of memantine. He testified about how memantine, obtained from outside the country, has helped his wife – enabled her to use seatbelts and flush toilets once again, to have conversations and share small jokes, and to have fewer inappropriate fits of anger. The changes have improved her quality of life and made his job as a caregiver easier, he explained.

Definition of severe patients

Some panel members also are concerned with how severe patients were defined – and at least one flatly stated that he believes moderate AD patients were included in the memantine trials. A panel member said, "This is not an academic discussion. The company is asking for an indication in a new area – severe AD – and we need to be sure not only that memantine is safe but also that it doesn't raise hopes or costs with no benefit."

Failure to meet one trial endpoint

One of the two U.S. trials met only one of the co-primary endpoints, but the other met both endpoints. This is troublesome to the FDA, but not necessarily a killer. The bigger issue appears to be that the drug only showed efficacy in severe patients subsets on one measure (SIB). Dr. Robert Temple, Director of the FDA's Office of Medical Policy,

Center for Drug Research and Evaluation, and also the Acting Director of Drug Evaluation 1 (which is in charge of oncology, neurology and cardiac drugs), cited the example of metropolol which had much better data in Europe than the U.S. Metropolol eventually got approved by the FDA, but he commented, "The only real answer to (this type of question) is more data."

Usefulness in mild/moderate AD

The only reference to mild/moderate was a description of the two monotherapy trials ongoing in mild/moderate AD: one by Forest and one by Lundbeck (which is marketing memantine in Europe with Merz), both of which should conclude about the same time. A Forest official said, "Our intent is -- if the studies support a new indication -- to apply to include mild AD."

An FDA official indicated that approval in moderate/severe AD probably should not be affected by the drug's success or failure in mild/moderate AD: "I supposed that if a drug already on the market for mild/moderate AD was shown not to be effective in moderate/severe AD, we probably wouldn't take it off the market...If you believe the moderate/severe data but have negative data in mild/moderate AD, could it be approved? We haven't considered that yet." A Forest official added, "If a drug were on the market for moderate/severe and it didn't work in mild, would you take it off the market? Or, is there a population getting a benefit?"

With respect to the failed trial of memantine+Aricept combination therapy in mild-to-moderate AD, a Forest official said, "That was an aggressive study. We recruited exceptionally fast (3-4 months) compared to the usual 6-9+ months…We believe the reason it was negative was…the lack of deterioration in the placebo group. In the ongoing monotherapy studies, we hope and anticipate the deterioration will be closer to the norm."

Safety question raised in a letter by a Washington University professor

Dr. John Olney sent a letter to panel members saying that memantine, especially in combination with an AchEI, can cause neurologic problems. Forest experts explained that NMDA receptor antagonists as a class can produce membrane-bound cytoplasmic vacuoles within the first day of dosing. Neuronal vacuolization progresses to necrosis in a proportion of neurons two or more days after NMDA antagonist exposure. However, those experts insisted this is a rodent-specific effect, only seen in rats and mice, and that it is a class effect of all NMDA antagonists. It is not observed in primates or in autopsies of humans who took the NMDA antagonist amantadine.

How clinicians will use this drug

This is one of the two key issues for the panel. The company argued that stopping progression is good, that patients and caregivers should not be led to expect improvement. A Forest expert said, "What clinicians should say to patients is that the slowing (in progression) you see with AChEIs is exactly what you will see with memantine. A small percentage of cases improve over time, but the overall effect of (memantine) in large part is similar to the AChEIs – **a** slowing (of progression) or symptomatic halting in the decline rather than a global increase in cognitive performance." However, an FDA official responded: "We don't think these trials are designed to look at the question of slowing progression. We think that if these studies show anything it is a symptomatic effect. In and of itself, we don't think that is a marker of progression. There is some suggestion on the part of some that -- based on a mechanism of action – there is a neuroprotective effect, and we don't think there is any evidence of neuroprotection in humans."

QUESTIONS POSED TO THE PANEL

Has the population for which the use of memantine is proposed been adequately identified in the studies included in this application? **YES by a unanimous vote.**

One panel member had a problem with the use of MMSE <10 as a definition of severe Alzheimer's Disease (AD), but the FDA's Dr. Temple defended the use of MMSE <10, saying it was a predetermined and previously accepted definition. Another panel member had a problem with the use of a retrospective classification in the Latvian memantine study (9403).

A third panel member worried about what the FDA would do if memantine is approved for severe AD and future trials show no benefit in mild-moderate AD. Dr. Temple responded, "For mysterious reasons a drug may work only in more severe forms of a disease. I can't imagine why, but you never know. We wouldn't particularly worry about that… You would try to point out in the labeling that it didn't seem to work in milder disease, but you don't not approve something in more severe disease because it doesn't seem to work in milder disease." The FDA's Dr. Katz agreed, "There are plenty of examples of drugs approved for a restricted portion of the disease population…so there is plenty of precedent with no particular obligation that the drug be shown to be effective in the entire universe of the named disease."

Dr. Temple indicated that Forest would be watched carefully to be sure it didn't claim that memantine is better than another drug, but the company would, if memantine is approved, be able to have a claim no one else has.

Are the designs of the key studies in this application adequate for evaluating the efficacy of memantine for the proposed indication? In particular, are the instruments used to evaluate efficacy in these studies appropriate for patients with moderate-to-severe AD? YES by a unanimous vote on both parts of this question.
However, there were reservations with the Latvian study and the state-of-the-art of tests in AD, especially severe AD.

Has substantial evidence of the effectiveness of memantine for the proposed indication been demonstrated by the studies included in this application? YES by a unanimous vote.
Forest submitted three studies in support of its application for memantine, and the FDA wanted to know which memantine studies panel members thought were crucial, how problematic the study done in Latvia (Study 9403) was, and if there was substantial evidence of efficacy without the Latvian study. The chairman of the panel answered, "The U.S. studies were key, but the CIBC in one was not significant, meaning to me that it actually wouldn't qualify as a pivotal trial – but the significance was p=.06, which made it awfully close, so my personal thinking was that the Latvian study was very useful in overcoming that." A neurologist on the panel said, "We don't analyze in a vacuum…I don't think that is a fair approach to this. I'm bothered by some of the borderline results and some scale issues, but I think on the whole there is some suggestion of efficacy. But you can't throw out information when you try to make that kind of interpretation. If it was that easy, we didn't need to discuss it; we just could have looked at p-values."

Study 9403 (Latvia)

Measurement	Prospective analysis (n=75)	By FDA-defined population (n=63)
BGP-care	p<.003	p=.002
CGIC	p=<.01	p<.001

Has substantial evidence of the safety of memantine for the proposed indication been demonstrated by the studies included in this application? YES by a unanimous vote.
However, the chair added after the vote, "I take exception to any claims that memantine is safer than placebo…We voted on four things, and it may look like we are in absolute, complete, enthusiastic agreement, but as the entire committee has certain concerns in all of the areas we were asked to vote on...This is another way of saying that I'm glad this is the FDA's job and not the committee's." Another panel member cautioned, "I'm concerned with longer term use and potential drug interactions as patients go on antipsychotics or other medications."

THE OUTLOOK

As expected, Forest officials were very happy with the outcome of the advisory committee meeting. They are excited about bringing Namenda (the brand name for memantine) to market. However, Namenda will not be on the market before the end of the year at the earliest, and probably not until late 1Q04. Even if Forest gets an approval by the memantine PDUFA date of October 19, 2003 (which means an FDA decision by Friday, October 17th), the company needs two or three months for batch testing and production.

The memantine 10 mg tablets will be made at the Forest plant in Ireland and packaged in the U.S. Forest official said they company already has cGMP on the plant for this product. They also claimed there will be no supply issues with Namenda – that they can make all they can sell.

It also is quite likely that Forest will get an approvable letter rather than an approval by October 17th. An FDA official said, "In our division, we typically give approvables, not approvals." Forest plans to answer the FDA in "weeks not months" as has been its practice with other drugs. Thus, Forest officials are predicting commercial availability in 1Q04. The company plans to make the drug available to pharmacies before its advertising campaign and formal launch is ready. An official said, "We will get it to pharmacies as opposed to waiting for our formal launch activities to be finalized…We are not waiting for the advertising campaign and all the bells and whistles at launch to make it available to the marketplace."

An FDA official said the ongoing memantine mild/moderate AD trials are "not a critical factor in our decision process." Yet, there are likely to be serious label discussions because Forest is expected to want more than the FDA is planning to give in terms of label claims. An FDA official said, "The label on monotherapy or combination therapy is still an issue." A Forest official said, "Most of our labeling is pretty boilerplate, in common with past AD drugs, so the agency is not unfamiliar with that, and they've acknowledged that to us in independent conversations. A lot of the discussion will be on the description of the trials in the trials section (of the label)…I don't think we will get a moderate AD only label. I think the agency will label by MMSE…If we got only moderate AD, we would still launch the product…We would market under the moderate label if we were dealt that, but we would argue hard for moderate-to-severe." Forest expects to get approval as "add-on" therapy as well as monotherapy.

In preparation for a launch, Forest has already started talking with some of the managed care firms. An official said, "We've started working with some managed care folks, but I can't say more than that…except that we have generally been successful with other products on that (reimbursement)." ♦