

## MEMORANDUM

DATE: August 27, 2003

FROM: Director  
Division of Neuropharmacological Drug Products/HFD-120

TO: Members  
Peripheral and Central Nervous Systems Drugs Advisory  
Committee

SUBJECT: Cover Memo for PCNS Advisory Committee Meeting on 9/24/03 to Discuss NDA 21-487, for the use of Memantine in Patients with Moderate to Severe Dementia of the Alzheimer's Type

As you know, on September 24, 2003, the PCNS Advisory Committee will discuss NDA 21-487, for the use of Memantine in Patients with Moderate to Severe Dementia of the Alzheimer's Type (DAT), which was submitted by Forest Laboratories on 12/19/02. Memantine presumably acts by antagonizing the NMDA receptor, thereby interfering with the deleterious effects of excess glutamate release. The data to be discussed consists of three randomized placebo-controlled trials that enrolled patients with moderate to severe dementia of the Alzheimer's type, as well as safety data in this, and other related, populations.

As you also know, there are currently four approved treatments for patients with dementia of the Alzheimer's type (all presumably producing their effects by inhibiting acetylcholinesterase), but all four are approved for patients with mild to moderate disease. This application represents the first application for patients with moderate to severe disease, and for this reason, we have chosen to discuss this application with the committee.

In this package, we have included this summary memo, as well as a detailed review of the effectiveness data performed by Dr. Ranjit Mani, medical officer in the division, and a separate statistical review of these studies performed by Dr. Tristan Massie, of the Division of Biometrics. In addition, we are including a detailed review of the safety data, performed by Dr. Jerry Boehm, of the division's Safety Team. Finally, we are including several articles from the literature that discuss various issues related to assessing cognitive function in this population. In this memo, I will very briefly describe the relevant efficacy and safety data, and present the issues we would like the committee to discuss and consider at the 9/24/03 meeting. Under separate cover, you will be receiving the sponsor's briefing book.

## Effectiveness

As noted above, the sponsor has submitted the results of three randomized controlled trials that they believe establish that memantine is effective as a treatment for DAT.

### Study MRZ 9605

This was a 28 week, randomized, placebo controlled, double blind parallel group study in patients with moderate to severe DAT, conducted at 32 centers in the US. Patients were required to have a diagnosis of probable AD, and were required to have a baseline MMSE score of 3-14. The primary outcome measures were the change from baseline in the ADCS-ADL (Alzheimer's Disease Cooperative Study-Activities of Daily Living, a 45 item scale, a subset of which consisting of 19 items was used in this study; these 19 items were selected to be most appropriate for moderate to severely ill patients, and the range is from 0 [worst] to 54 [best]; see Dr. Mani's review, page 17 for a complete description of the items), and the CIBIC-plus (a standard physician rated measure of global functioning routinely used as a co-primary outcome measure in other studies of treatments for DAT; the scale ranges from 1, Markedly Improved to 7, Markedly Worse—a score of 4 indicates No Change). There were no measures of cognitive function designated as primary in this study, although numerous secondary measures were assessed, including the MMSE and SIB (the Severe Impairment Battery, a 51 item, 9 sub-scale measure designed for severely ill patients that assesses attention, orientation, language, memory, praxis, visuospatial perception, construction, social skills, and orientation to name; the total score ranges from 0-100, with higher scores indicating better functioning). Because the standard for approving drugs to treat mild to moderate DAT includes a showing of a statistically significant between treatment difference on both a global and a cognitive measure, we examined the results of between treatment comparisons on the SIB in addition to the protocol specified primary outcomes, which are both measures of global functioning.

In this study, patients were randomized to either memantine 10 mg BID (N=126; 97 completers) or placebo (N=126; 84 completers). The results for the intent to treat (ITT), last observation carried forward (LOCF) analyses were as follows:

	Placebo	Memantine	P-value
Mean CIBIC	4.73	4.48	0.064
Mean Change From Baseline ADCS-ADL	-5.08	-3.02	0.022
SIB	-9.84	-4.46	0.0003

Because an MMSE of about 10 is the usual lower limit of baseline MMSE scores allowable in studies of patients with mild to moderate DAT, we examined the results of these outcome measures in the population of patients whose baseline MMSE scores were less than 10 (in other words, in patients ordinarily not included in the previous studies of the approved treatments and who are considered to have “severe” DAT); the results are as follows:

	Placebo	Memantine	P-value
Mean CIBIC (<10; N=145)	4.80	4.68	0.53
(>10; N=91)	4.75	4.23	0.02
Mean ADL (<10; N=152)	-5.6	-4.5	0.27
(>10; N=95)	-4.6	-0.6	0.01
SIB (<10; 152)	-11.8	-5.8	0.009
(>10; 95)	-7.6	-0.8	0.009

### **Study MRZ 9403**

This was a 12 week, randomized, double-blind, placebo controlled parallel group study in patients with moderate to severe DAT or vascular and/or mixed dementia (baseline MMSE of 0-9), performed in 7 centers in Latvia.

In this study, patients were randomized to receive either memantine 10 mg once a day (N=82, 78 completers), or placebo (N=84, 80 completers). The protocol specified primary outcome measures were the change from baseline in the BGP Care Dependency Subscale of the BGP and the CGI-C (this latter was to be dichotomized). Retrospectively, and after the initial results were known, the results of the BGP Cognitive Subscale were analyzed (this was a retrospectively created scale consisting of all of the items in the BGP that were considered to directly measure “cognitive” functions; see Dr. Mani’s review, page 18-19 for a complete description of this scale). The results of the ITT, LOCF analyses for all of the patients enrolled are as follows:

	Placebo	Memantine	P-value
Mean CGI-C	3.5	3.1	<0.001
Mean Change From Baseline BGP-Depen	-3.3	-5.3	0.012
Mean Change From Baseline BGP-Cog	-1.1	-1.9	0.001

In this study, patients with DAT and vascular dementia were enrolled. Retrospectively, the sponsor categorized the patients on the basis of a their baseline Hachinski scores; patients with Hachinski scores of less than or equal to 4 were considered to have had DAT. The following table gives the results for patients diagnosed with DAT (N=79):

	Placebo	Memantine	P-value
Mean CGI-C	3.5	3.1	0.003
Mean Change From Baseline BGP-Depen	-2.8	-5.8	0.003
Mean Change From Baseline BGP-Cog	-1.0	-2.0	0.007

In this study, 86 patients (about half the total enrollment) had CT scans performed at entry. In an attempt to independently assess whether or not the sponsor's classification of disease (DAT or VaD) was accurate (recall that this was done retrospectively according to baseline Hachinski score), we read the translated descriptions of the CT scans in these patients without knowledge of treatment assignment in these 86 patients. While the reports were frequently incomplete and inadequate, we found 39 instances in which the radiological diagnosis could reasonably be considered to differ from the diagnosis made by the sponsor (the results of this examination are appended to this memo).

### **Study MEM-MD-02**

This was a 24 week, randomized, placebo controlled, double-blind, parallel group study in patients with moderate to severe (baseline MMSE of 5-14) DAT who were receiving donepezil (an approved cholinesterase inhibitor), performed in 38 centers in the US. The primary outcome measures in this study were the change from baseline in the SIB and the ADCS-ADL.

In this study, patients were randomized to memantine 10 mg BID (N=202; 172 completed) or placebo (N=201; 150 completed), added on to a stable dose of donepezil (either 5 or 10 mg/day). The results of the ITT, LOCF analyses are as follows:

	Placebo	Memantine	P-value
Mean Change From Baseline ADCS-ADL	-3.4	-2.0	0.028
SIB	-2.5	0.9	<0.001

For purposes of comparison to other studies, the following results on several selected secondary measures are presented below:

	Placebo	Memantine	P-value
Mean CIBIC-Plus	4.6	4.41	0.027
Mean Change From Baseline BGP-Depen	2.3	0.8	0.001
Mean Change From Baseline BGP-Cog	0.5	0.2	0.035

Again, in this study, patients with baseline MMSEs of 10 or greater (“moderate” disease) were enrolled. In order to examine the effects of memantine on “severe” patients (MMSE <10), the following analyses were performed:

	Placebo	Memantine	P-value
Mean ADL (<10; N=161)	-4.6	-2.8	0.17
(>10; N=234)	-2.4	-1.1	0.08
SIB (<10; 161)	-6.2	0.1	0.002
(>10; 233)	0.0	1.8	0.05

## Safety

The sponsor has submitted safety experience in 1,748 patients enrolled in trials in dementia (DAT and VaD) and neuropathic pain; in 487 subjects in clinical pharmacology studies, and in over 4,000 patients enrolled in on-going and

completed trials in other indications, as well as post-marketing reports from what they estimate to be about 400,000 person-years of use.

Of the 1748 patients enrolled in trials of dementia or neuropathic pain, a total of 940 patients were enrolled in placebo-controlled dementia trials; of these 940, 355 were in trial of DAT, while an additional 97 were in trials in which patients with DAT or VaD were enrolled. The median duration of treatment in the dementia controlled trials was 171 days.

In controlled trials in patients with dementia, there were 18 deaths in the memantine treated group (1.9%) compared to 21 deaths in placebo patients (2.3%). The mortality rate in memantine treated patients was 4.6/100 pt-yrs, compared to 5.5/100 pt-yrs in placebo treated patients. There were no deaths that appeared to be related to treatment with memantine. In open-label dementia studies, the mortality rate was 7.9/100 pt-yrs, similar to that seen in the controlled trials. In open-label studies, the risk for the group that had received memantine in the controlled trials was similar to the risk in the group that had original received placebo (3.6% vs 3.8%, respectively).

In controlled trials in dementia, the risk for a serious adverse event (SAE) was 14.6% in the placebo group, and 13.5% in the memantine-treated group. The respective rates were 35.5/100 pt-yrs and 32.7/100 pt-yrs. The risk of an SAE in the open-label dementia studies was 17.4%, with a rate of 36.6/100 pt-yrs. There were no obvious drug-related SAEs of concern; in open-label studies, the risks were similar in the groups treated in the controlled trials with placebo or memantine.

The risk of discontinuation secondary to an adverse event from the controlled trials in patients with dementia was 11.5% for the placebo patients and 10.1% for the memantine-treated patients. The respective rates were 27.8/100 pt-yrs and 24.4/100 pt-yrs. In the open label experience, the risk for discontinuing secondary to an adverse event was 10.7%, with a rate of 22.6/100 pt-yrs; again, in open-label studies, the risks were similar in the groups treated in the controlled trials with placebo or memantine.

There were a number of adverse events seen more commonly in memantine treated patients compared to placebo treated patients in dementia studies (see, for example, Dr. Boehm's review, pages 33-5), but there were only two adverse events seen at a rate twice that of placebo in all dementia studies, and six in studies of patients with DAT:

	All dementia		DAT	
	Pbo	Mem	Pbo	Mem
Pain	0.9%	2.6%	0.3%	2.3%
Dyspnea	1%	2%		
Headache			2%	5.6%
Prostatic Disorder			0%	3.8%
Gait Abnormal			1.5%	3%
Cardiac Failure			0%	2%
Urinary Frequency			1%	2%

There were no cases of clinical concern among these reports.

Evaluation of the adverse event profile of memantine in indications other than dementia revealed no signals of concern.

There appeared to be no significant changes in vital signs, EKG interval data, or laboratory tests.

### **Comments**

The sponsor has submitted the results of three randomized controlled trials that they believe establish that memantine is effective as a treatment for patients with moderate to severe dementia of the Alzheimer's type. In addition, they have submitted safety data that they believe support the view that memantine will be safe in use, given appropriate labeling.

The data submitted raise a number of questions that we would like the Committee to discuss at the meeting on the 24<sup>th</sup>. The questions fall into two general categories: 1) questions related to the specific data for memantine, and 2) questions related to the generic study of drugs to treat moderate to severe dementia.

### **Memantine-specific questions**

The data in this application raise several specific questions.

First, there are questions related to Study MRZ 9605.

In this study, there was no cognitive scale designated as a co-primary outcome. While we chose to present the results of the SIB (which was not only nominally "positive", the significance persists in the face of any reasonable adjustment for multiple comparisons), at least one other cognitive measure, the MMSE, was also performed in this study, and the between-treatment comparison on this outcome was not even nominally positive ( $p=0.19$ ). We would like the committee to discuss this issue.

Further, the two co-primary outcomes were essentially global outcomes, and one, the CIBIC-plus, did not reach the traditional level of statistical significance ( $p=0.064$ ). We are very interested to know the committee's view of the lack of significance on this protocol specified primary outcome measure (we have no reason to believe, for example, that this outcome is any less valid in this population than the ADCS-ADL).

Perhaps of more concern, however, is the finding that patients with MMSE scores of less than 10, when analyzed as a separate group, fail to demonstrate significance on either of the primary global measures. While this is, of course, a retrospectively created subgroup, the lack of significance may not be related simply to a lack of power, given that the subgroup with higher MMSE scores was smaller, and the analyses for the CIBIC and ADL were positive in this subgroup. We are very interested to know whether or not the Committee believes that this finding raises serious questions about the value of this treatment in severe patients, the one group of patients for whom this treatment is proposed to be uniquely effective.

The Latvian study raises many questions.

The various scales used were relatively non-standard, crucially, the "cognitive" scale was created after the data had been analyzed, and, in any event, the items included in this "scale" are not necessarily equivalent to the items included in more typical cognitive measures (there is, of course, no data on the validity of this "cognitive" measure in this population). Further, our independent review of the CT scans performed suggests that the method used to diagnose DAT or VaD (after the fact) was inadequate; for half of the patients who had CT scans performed, we concluded that the CT scan suggested that the diagnosis made via the Hachinski score was wrong. We are very interested to hear whether or not the Committee feels that this study can be considered a valid source of evidence of the effectiveness of memantine as a treatment for patients with moderate to severe DAT.

### **Generic Issues**

Given that this is the first application submitted to the Agency for this population, we have a number of issues that we would like the Committee to discuss that are pertinent to the requirements that should be imposed on any sponsor wishing to obtain a claim in this setting.

As is well known, to date, treatments for patients with DAT have been required to demonstrate a significant effect on two co-primary outcome measures: a specific measure of cognitive function (in order to assess the "core" symptoms of the disease), and a measure of global patient functioning (in order to ensure that any effect seen on the cognitive measure has clinical meaning to the patient). In the

case of all four currently approved treatments, these measures have been the ADAS-Cog and the CIBIC-Plus. We have maintained that this same approach is appropriate for drugs to treat patients with severe DAT as well, although some have argued that, given the patients' condition, a formal assessment of cognitive functioning (or less often, global functioning) is not necessarily appropriate. We are interested in the Committee's views on this fundamental issue of trial design.

Further, and more specifically, the sponsor has used (in two of the trials) a specific measure of cognitive function, the SIB, a scale specifically designed to assess cognitive function in more severely impaired patients. We are interested in the Committee's views on the appropriateness of this scale as a cognitive measure in this population. In addition, the "global" measure in two studies was the ADCS-ADL, another scale that has not been used as a primary global measure in previous studies (of approved drugs). We would also like to hear the Committee's views about the appropriateness of the use of this scale to assess global functioning in this population.

While we are asking for the Committee's input on these specific issues, we are, of course, eager to hear if there are any other issue(s) the Committee feels should be discussed.

I would like to thank you in advance for your work on both issues to be discussed at the meetings, and I look forward to seeing you in September.

# NDA 21487

## Memantine

### Study 9403

#### Distribution Of Dementia Subgroups Based On CT Scan And Hachinski Ischemic Scale

Patient #	Assignment based on CT scan report (Reviewer)	Sponsor assignment based on Hachinski Ischemic Scale
001	Alzheimer's Disease	Vascular dementia
003	Vascular dementia?	Alzheimer's Disease
005	Vascular dementia?	Vascular dementia
006	Alzheimer's Disease	Alzheimer's Disease
007	Alzheimer's Disease	Vascular dementia
008	Alzheimer's Disease	Alzheimer's Disease
009	Alzheimer's Disease	Alzheimer's Disease
010	Vascular dementia?	Alzheimer's Disease
011	Neither (head trauma)	Alzheimer's Disease
018	Alzheimer's Disease	Vascular dementia
019	Alzheimer's Disease	Alzheimer's Disease
020	Vascular dementia	Alzheimer's Disease
022	Vascular dementia	Vascular dementia
024	Vascular dementia?	Vascular dementia
028	Alzheimer's Disease	Alzheimer's Disease
031	Alzheimer's Disease	Alzheimer's Disease
036	Alzheimer's Disease	Alzheimer's Disease
133	Alzheimer's Disease	Vascular dementia
135	Vascular dementia?	Vascular dementia
136	Alzheimer's Disease	Alzheimer's Disease
188	Alzheimer's Disease	Vascular dementia
192	Alzheimer's Disease	Alzheimer's Disease
037	Alzheimer's Disease	Vascular dementia
038	Vascular dementia?	Vascular dementia
039	Alzheimer's Disease	Alzheimer's Disease
040	Vascular dementia?	Vascular dementia
041	Vascular dementia	Vascular dementia
044	Alzheimer's Disease	Alzheimer's Disease
045	Alzheimer's Disease	Alzheimer's Disease
046	Alzheimer's Disease	Alzheimer's Disease
049	Vascular dementia?	Vascular dementia
050	Alzheimer's Disease	Alzheimer's Disease
054	Alzheimer's Disease	Vascular dementia
127	Vascular dementia?	Alzheimer's Disease
128	Alzheimer's Disease	Alzheimer's Disease
129	Alzheimer's Disease	Alzheimer's Disease
132	Vascular dementia?	Alzheimer's Disease
142	Alzheimer's Disease	Vascular dementia
146	Vascular dementia?	Alzheimer's Disease
196	Alzheimer's Disease	Alzheimer's Disease
197	Alzheimer's Disease	Alzheimer's Disease
198	Alzheimer's Disease	Alzheimer's Disease
055	Alzheimer's Disease	Vascular dementia
056	Alzheimer's Disease	Vascular dementia
058	Alzheimer's Disease	Alzheimer's Disease
059	Alzheimer's Disease	Vascular dementia
060	Alzheimer's Disease	Vascular dementia
061	Vascular dementia?	Vascular dementia
062	Vascular dementia? Previous craniotomy	Alzheimer's Disease
064	Unclear. Previous craniotomy with porencephalic cyst on the same side	Vascular dementia

065	Alzheimer's Disease	Vascular dementia
066	Alzheimer's Disease	Vascular dementia
067	Alzheimer's Disease	Alzheimer's Disease
068	Alzheimer's Disease	Vascular dementia
069	Alzheimer's Disease	Vascular dementia
070	Vascular dementia	Vascular dementia
071	Alzheimer's Disease	Vascular dementia
072	Alzheimer's Disease	Vascular dementia
073	Alzheimer's Disease	Vascular dementia
074	Alzheimer's Disease	Vascular dementia
076	Alzheimer's Disease	Vascular dementia
077	Vascular dementia	Vascular dementia
078	Alzheimer's Disease	Vascular dementia
109	Vascular dementia?	Vascular dementia
111	Alzheimer's Disease	Vascular dementia
112	Vascular dementia?	Vascular dementia
114	Alzheimer's Disease	Vascular dementia
115	Alzheimer's Disease	Vascular dementia
116	Alzheimer's Disease	Vascular dementia
117	Alzheimer's Disease	Alzheimer's Disease
119	Vascular dementia	Alzheimer's Disease
120	Alzheimer's Disease	Alzheimer's Disease
123	Alzheimer's Disease	Alzheimer's Disease
124	Unclear. Lesion in right occipital lobe attributed to trauma	Alzheimer's Disease
079	Alzheimer's Disease	Vascular dementia
080	Alzheimer's Disease	Alzheimer's Disease
081	Alzheimer's Disease	Alzheimer's Disease
082	Alzheimer's Disease	Alzheimer's Disease
083	Alzheimer's Disease	Alzheimer's Disease
085	Alzheimer's Disease	Vascular dementia
086	Alzheimer's Disease	Alzheimer's Disease
087	Alzheimer's Disease	Alzheimer's Disease
088	Vascular dementia	Vascular dementia
089	Alzheimer's Disease	Vascular dementia
090	Alzheimer's Disease	Alzheimer's Disease
093	Vascular dementia	Alzheimer's Disease
094	Alzheimer's Disease	Alzheimer's Disease
099	Alzheimer's Disease	Alzheimer's Disease
101	Alzheimer's Disease	Alzheimer's Disease

The NINDS-AIREN radiological criteria for vascular dementia were used to the extent possible. The reports were insufficiently descriptive in many instances where vascular lesions were present, to apply the criteria satisfactorily