MEM-MD-02 INVESTIGATOR LIST

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MEM-MD-02 INVESTIGATOR LIST

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MEM-MD-02 INVESTIGATOR LIST

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MEM-MD-02 INVESTIGATOR LIST

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MEM-MD-02 INVESTIGATOR LIST

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MEMORANDUM

DATE: October 11, 2003

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

TO: File, NDA 21-487

SUBJECT: Memo for Recommendation of Action on NDA 21-487, for the use of Memantine in Patients with Moderate to Severe Dementia of the Alzheimer's Type

NDA 21-487, for the use of Memantine in Patients with Moderate to Severe Dementia of the Alzheimer's Type (DAT), 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 application 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. In addition, the requisite pre-clinical, CMC, and biopharmaceutics data have been submitted.

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.

The application has been reviewed by Dr Ranjit Mani, medical officer (reviews dated 10/2/03), Dr. Gerard Boehm, safety reviewer (reviews dated 8/20/03 and 9/26/03), Dr. Kathy Haberny, pharmacologist (review dated 10/9/03), Dr. Katherine Bonson, Controlled Substances Staff (review dated 9/30/03), Dr. Tristan Massie, statistician (review dated 9/29/03), Dr. Vaneeta Tandon, Office of Clinical Pharmacology and Biopharmaceutics (review dated 10/2/03), Dr. Rajeshwari Sridhara, carcinogenicity reviewer (review dated 8/25/03), Janusz Rzeszotarski, chemist (review dated 8/20/03), and Dr. Armando Oliva, Neurology Team Leader (memo dated 10/2/03). The clinical team recommends that the application be approved.

In this memo, I will very briefly describe the relevant efficacy and safety data, and present the division's recommendation for action on this application.

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 moderate to severe 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 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.

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 trials 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 originally 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.

Other Disciplines

There were no other significant issues, although various reviewers have requested several Phase 4 commitments. Specifically:

1) A final study report of an on-going renal impairment study
2) A protocol for a study in patients with hepatic impairment
3) A protocol to assess the induction potential of memantine
4) A re-analysis of EKG data by a central laboratory (including data from Study MD-06A, which was not previously submitted
5) Submission of results of eye examinations in on-going studies

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.

Because this is the first application submitted to the Agency that proposes a treatment for patients with moderate to severe dementia, the application was discussed at a meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee on September 24th. At that meeting, we asked the Committee to vote on the following four questions;

1) Has the population for which the use of memantine is proposed been adequately identified in the studies in this application?

There was considerable discussion at the meeting about whether or not patients with severe dementia had been enrolled in these trials. Specifically, while the range of MMSE scores that patients were permitted to have in order to be enrolled in these studies clearly permitted patients into these trials with lower scores than those permitted into the studies of the currently approved drugs (in this application, patients with MMSE scores of 3-5, and even 0, were enrolled, whereas in the NDAs for the currently approved drugs, the lower MMSE limit was usually 10), there was discussion about whether or not this criterion adequately identified patients with severe disease. The Committee voted unanimously (8-0) that there were patients enrolled in these trials who were, indeed, severely demented. I agree. In my view, MMSE scores below 10 identify patients whose cognitive dysfunction, at least, is severely impaired; at the very least, their cognitive function is worse than that of the patients enrolled into the studies in the previously approved NDAs. Other measures used in these studies also documented that (a subset of) these patients were severely impaired.

2) Are the designs of the key studies, and the instruments used to evaluate patients, appropriate to evaluate the effectiveness of a treatment of patients with moderate to severe AD?

The Committee again felt that the studies were adequate for the purpose, although there was, it appeared, general agreement that there was no adequate assessment of cognitive function in the Latvian study (the sponsor also admitted as much). The division raised the question about whether or not the ADSC-ADL was an adequate measure of functioning in this population, given that some of the items in the scale appeared to assess some dubious functions (e.g., ability to

watch television). Further, the question about small treatment differences on this scale was discussed. Specifically, the point was made that the traditional CIBIC-plus is a measure that, at least, purports to measure global patient functioning, and that even small changes on this scale are considered to reflect useful clinical gains, whereas the clinical meaning of small changes on the ADL are perhaps questionable. In answer to this last question, the sponsor noted that the permitted ratings for the specific items on this scale implied, by definition, meaningful clinical change. Further, they described the results by item, demonstrating that changes occurred in many, obviously clinically important, items. The Committee clearly felt that the scale was adequate to assess function in this population, and that the use of such a functional (or global measure) is necessary in this population. I agree that these studies (at least the two US studies) were adequate. I agree with the review team that the Latvian study was potentially problematic (we are not entirely confident that patients with AD were adequately identified and there was, effectively, no cognitive measure employed), but, to the extent that it is likely that a substantial number of AD patients were included, and the results on the global measures used were highly significant, the study is supportive of effectiveness in this population.

3) Has substantial evidence of effectiveness been submitted?

The Committee voted unanimously that substantial evidence of effectiveness had been submitted, but there was considerable discussion about the size of the treatment effect seen. Further, there was considerable discussion about the fact that in Study 9605, there was no evidence of an effect on the CIBIC-plus in patients with MMSE scores less than 10 (the severe sub-group), as there were no significant differences in this group on the ADL (although there was a slight numerical superiority in favor of drug on this latter measure). The lack of statistical significance in this sub-group seemed not to be a question of a lack of power to demonstrate such a difference; the treatments were statistically significantly different in the sub-group of patients with MMSE scores greater than 10, and this was a smaller sub-group than the less than 10 sub-group.

This point was of some importance, because it raised questions about the effectiveness of the treatment in the severe group, the very group for which the sponsor is seeking a unique claim. However, mitigating this finding was the fact that in this study (as well as in Study MD-02), there were strongly significant findings on the cognitive measure (SIB) in the severe sub-set, there were strongly significant findings on the global measures in Study 9403 (in which all patients were considered severely impaired), and there was clear numerical superiority on the ADL in Study MD-02, in which the severe sub-group was smaller than the moderate sub-group (the findings were not significant in either of these subgroups on the global measures).

There was also discussion about the fact that, in Study 9605, one of the two primary outcomes (recall that they were both "global" measures), did not reach statistical significance (the p-value for the between-treatment contrast was 0.064). However, the Committee noted that not only was there clear statistical significance on the ADL in Study MD-02 and on the global measures used in Study 9403 (which included the CIBIC-plus), but there was statistical significance on the CIBIC-plus in Study MD-02 (a secondary outcome, but prospectively designated as an important secondary outcome), and any reasonable adjustment for multiple comparisons in Study 9605 still yielded statistical significance in Study 9605 on the ADL, a co-primary outcome.

Given these considerations, the Committee felt that the data support the conclusion that the drug is effective in this population (Dr. Kawas, the chair of the Committee, explicitly stated that she would have had a difficult time concluding that an effect on function had been demonstrated without Study 9403 [the Latvian study], though this seemed to be a minority view.) I agree that the data do support the conclusion that the drug has an effect on both cognitive and functional outcomes.

4) Has the sponsor demonstrated that the drug is acceptably safe?

The Committee voted unanimously that adequate safety data had been submitted. I agree; there are no important safety concerns in the application, though we will ask the sponsor to provide additional analyses of the EKG data (see Dr. Boehm's safety review).

There is one other issue not specifically discussed by the Committee, but worth noting.

The two US studies were performed at a dose of 10 mg BID, while the Latvian study was performed at a dose of 10 mg QD. While the Committee relied, to some extent, on the data in this latter study (in particular, some members relied on the global findings in this study as strong support for the view that the drug has an effect on global functioning, and others relied on the fact that all of the patients in this study were clearly severely demented [the inclusion criteria required that patients have an MMSE score less than 10] to support the conclusion that the drug is effective in this population), as noted above, we are not entirely convinced about how many patients with AD were enrolled, and we note the lack of a valid measure of cognition in this study. While one could argue that the clear findings on the global measures (as well as on the retrospectively created "cognitive" measure) support the overall effectiveness of a 10 mg once a day dose, we believe that, given the uncertainties expressed, and given that 10 mg BID appears to be a very well tolerated dose, the appropriate daily dose should be 10 mg BID.

As noted, there are no important outstanding issues, although we will request some additional data in Phase 4. We have negotiated labeling with the sponsor, and we have agreed on a version of labeling.

For these reasons, then, I recommend that the sponsor be sent the attached Approval letter, with the appended agreed upon label.

/S/
Russell Katz, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
10/14/03 07:28:38 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: October 2, 2003
From: Armando Oliva, MD
To: Russell Katz, MD
Director, Division of Neuropharmacological Drug Products
Subject: Team Leader Memorandum for NDA 21-487, memantine

This application provides information to support the approval of memantine for the treatment of moderate to severe dementia of the Alzheimer's type in the United States. Dr. Mani provides the efficacy review. Dr. Boehm provides the safety review, and Dr. Massie provides the biometrics review. There are no CMC or pharmacology/toxicology issues that would preclude approval and I refer the reader to the respective reviews by Drs. Rzeszotarski and Haberny for additional information. I conclude that the sponsor has provided sufficient evidence to support efficacy and safety and I recommend approval of the application.

Memantine is an uncompetitive NMDA-receptor antagonist that binds preferentially to the NMDA receptor-operated cation channel. It is believed that glutamate may play a role in the pathogenesis of Alzheimer's Disease (AD). Non-clinical evidence suggests that blocking the NMDA receptor with memantine can provide protection from the neurotoxic effects of glutamate and improve memory and learning. Since NMDA receptor antagonism is associated with abuse potential in some cases (*e.g.*, PCP, ketamine), the controlled substances staff was consulted and they find little evidence for abuse potential.

Memantine has been marketed in Germany since 1982 for the treatment of Parkinsonism, cerebral and peripheral spasticity, and organic brain syndrome. The European Union approved memantine in 2002 for the treatment of Alzheimer's Disease.

In humans, memantine has an oral bioavailability of 100% and has a T_{max} of 4-6 hours. Food has no effect on absorption. C_{max} and AUC are dose proportional between 10-40mg. Memantine is extensively distributed in tissues and readily crosses the blood-brain-barrier. It is about 45% protein bound. The terminal half-life is 60-80 hours. It undergoes little metabolism and is excreted largely unchanged in the urine (75-90%). An acidic urine pH enhances renal excretion. The remainder is converted to three polar metabolites which are believed to be inactive. Memantine clearance is reduced in renal impairment. Memantine has minimal inhibition of CYP P450 isoenzymes, and does not have pharmacokinetic or pharmacodynamic interactions with donepezil.

The application contains efficacy data from three randomized-controlled trials: MRZ 9605 (hereafter 9605), MEM-MD-02 (hereafter MD02), and MRZ 9403 (hereafter 9403). Before I discuss the design and results of these studies, I describe the various primary outcome measures that were used in these pivotal trials. Dr. Mani describes these scales in greater detail in his review starting on page 16. He also details the various secondary outcome measures used in these studies, which I do not discuss in this memo.

SIB: Severe Impairment Battery. This is a measure of cognition in severely demented patients. It contains 9 subscales assessing attention, orientation, language, memory, praxis, visuospatial perception, construction, social skills and orientation to name. Possible scores are 0-100 with higher scores indicating better cognitive function.

ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living. This is a measure of activities of daily living; a functional scale. In the full version, the investigator rates 45 items using information obtained from the caregiver. The "modified" ADCS-ADL, as used in these studies, uses 19 items selected to fit the expected activities of patients with moderate-severe AD (eg, eating, walking, toileting, etc.). Possible scores for the modified ADCS-ADL ranged 0-54, with higher scores indicating better function.

CIBIC-Plus: Clinician's Interview Based Impression of Change-Plus. This is the standard global 7-point scale used in many AD studies. It ranges from 1 (markedly improved) to 7 (markedly worse).

CGI-C: Clinician's Global Impression of Change. This is similar to the CIBIC-Plus except that the rater has access to all information (including results of psychometric test scores and physical examination results) at baseline when the severity of the disease is assessed (Clinical Global Impression of Severity – CGI-S). Subsequent ratings are based only on patient assessment and information provided by the caregiver.

BGP: Behavioral Rating Scale in Geriatric Patients. This is a 35-item clinician-rated measure that assesses behavior including mood, basic cognitive functions, mobility, and activities of daily living. Each item is rated 0-2, with 2 indicating the worst level of functioning. Rating is based on direct observation by the rater. The BGP has four standard subscales: Care Dependency, Aggressiveness, Composite (physical disability+depression+mental disability), and Inactivity subscales.

The BGP Care Dependency subscale comprises 23 of the 35 items in the entire BGP. Each item represents either activities of daily living or behavior. The maximum score is 46 with higher scores indicating a worse level of function.

An ad-hoc and post-hoc subscale of the BGP Care Dependency subscale is termed the BGP Cognitive Subscale. This was used in one of the pivotal studies. It consists of 5 items of the 23-item BGP Care Dependency subscale. The maximum score is 10. The items are:

- The patient makes himself understood (always, sometimes, rarely)
- The patient finds his way in the nursing home (generally yes, some ways yes/no, generally no)
- The patient understands in what home or clinic he is (always, sometimes, rarely)
- The patient knows the names of the staff (more than one, only one, none)
- The patient understands what you communicate with him (always, sometimes, rarely)

I would like to point out that our biostatistician, Dr. Massie, has confirmed the results presented by the sponsor. In some cases, the p-values are slightly different (eg, the sponsor's p-values for study 9605 differ slightly from Dr. Massie's since the sponsor included patients with no post-baseline efficacy measures in the "ITT" population by carrying the baseline value forward. Dr. Massie's ITT analysis consists of patients with baseline and at least one post-baseline primary efficacy measure). However, the differences do not materially affect the overall conclusions. Throughout this memo, I present the results as described by Dr. Mani, and refer to Dr. Massie's review whenever it provides further insight into the data.

Study 9605

9605 was a randomized, double-blind, placebo-controlled, parallel arm study conducted at 32 centers in the United States. It compared memantine with placebo in patients with moderate to severe AD.

Subjects enrolled in this study met NINCDS-ADRDA diagnostic criteria for AD and had baseline Mini Mental Status Examination (MMSE) scores of 3-14 (out of a possible 30), so they fell in the moderate to severe range of impairment. Excluded from the trial were those taking acetylcholinesterase inhibitors or other drugs intended to treat cognitive dysfunction. Subjects were randomized to receive either memantine 10mg bid or placebo for 28 weeks. The first 4 weeks of double-blind treatment included a titration regimen of 5mg/wk to reach 10mg bid by week 4.

The primary efficacy measure was the modified ADCS-ADL (functional) and the CIBIC-Plus (global). Among the seven secondary measures was the Severe Impairment Battery (SIB), a cognitive scale.

The primary and secondary analyses were conducted on the ITT population using an LOCF approach to impute missing data, using the Wilcoxon-Mann-Whitney test for independent samples.

A total of 252 subjects were enrolled in the study and exactly half received memantine. A total of 97 memantine-treated subjects and 84 placebo-treated subjects completed the study. Actual baseline MMSE scores ranged 1-14. The treatment groups were broadly comparable in regard to mean age and baseline cognitive and functional status.

The results of the primary analyses and the SIB are shown in Table 1 (taken from Dr. Mani's review, page 22)

Table 1: Study 9605 – Key Efficacy Results

	LOCF Analysis			OC Analysis		
	Memantine (n = 126)	Placebo (n = 126)	p-value*	Memantine (n = 97)	Placebo (n = 84)	p-value*
CIBIC-Plus	4.48	4.73	0.064	4.38	4.74	0.025
ADCS-ADL	-3.02	-5.02	0.022	-2.49	-5.48	0.003
SIB	-3.93	-9.84	< 0.001	-4.46	-10.16	0.002

*p-values are based on Wilcoxon-Mann-Whitney test for between treatment comparisons

The primary efficacy analysis compared mean scores in the CIBIC-Plus. The between treatment group difference in the mean CIBIC-Plus scores was small (0.25 points) and favored memantine. The analysis did not reach statistical significance (p=0.064). As Dr. Massie notes in his review, the observed cases population did show a significant treatment effect on the CIBIC-Plus, but dropouts did worse than completers, particularly, in the memantine group. He concludes that the Observed Cases population does not give the complete picture and may be slightly biased in favor of memantine.

The between-group difference in the mean change from baseline of the modified ADCS-ADL was a modest 2 points in favor of memantine. This comparison was statistically significant (p=0.022). Even if one corrects for two comparisons in the primary analyses using a conservative Bonferroni correction, the finding on this functional scale remains significant.

Analysis of the change from baseline in mean SIB scores yielded a between group difference of 5.91 points that favored memantine and was highly nominally significant at p=0.0003. Although this was not a primary measure, the finding in the SIB is sufficiently robust that it would remain significant even after correction for multiple secondary comparisons. It is notable that patients as a group did not improve while on memantine, but rather deteriorated less than their placebo-treated counterparts.

Dr. Massie performed a subgroup analysis of these endpoints according to baseline MMSE scores (<10 and ≥10). This subgroup analysis is of particular interest because patients with MMSE<10 were excluded in the dementia trials of currently approved treatments. Memantine would be the first approved treatment for this subgroup.

Treatment effects were greater in the subgroup of patients with MMSE scores ≥ 10 for the two primary endpoints, but were about the same for the SIB in both subgroups.

Table 2: Study 9605 - Mean Outcome Measures (LOCF) by MMSE and Treatment

Variable	Group	Treatment Code	n	Baseline	Endpoint</thead><tbody>	Treatment Effect p value *
Primary						
ADL	<10	Placebo	73	25.5 (11.9)	-5.6 (6.5)	0.2643
	<10	Memantine	79	24.3 (9)	-4.5 (6.7)	
	>= 10	Placebo	50	30.7 (8.4)	-4.6 (6.1)	0.0080
	>= 10	Memantine	45	31 (7.8)	-0.6 (6.4)	
CIBIC+	<10	Placebo	70	N / A	4.80 (1.06)	0.5341
	<10	Memantine	75	N / A	4.68 (1.10)	
	>= 10	Placebo	48	N / A	4.75 (1.14)	0.0206
	>= 10	Memantine	43	N / A	4.23 (1.09)	

Variable	Group	Treatment Code	n	Baseline	Endpoint</thead><tbody>	Treatment Effect p value *
Secondary						
SIB	< 10	Placebo	73	58 (19.4)	-11.8 (14)	0.0082
	< 10	Memantine	79	55 (20.4)	-5.8 (12.6)	
	>= 10	Placebo	50	83.7 (8.8)	-7.6 (12.5)	0.0073
	>= 10	Memantine	45	84.8 (11.3)	-0.8 (7.9)	

* based on Wilcoxon Rank Sum Test

In summary, this study supports the efficacy of memantine in moderate-severe dementia of the Alzheimer's type by virtue of positive results on a cognitive scale, the SIB, and a functional scale, the modified ADCS-ADL. Subgroup analysis does support an effect on the SIB in the severely impaired patients, but an effect is not confirmed by the global or functional measures in that study.

Study MD02

MD02 was a randomized, double-blind, placebo-controlled parallel arm study conducted at 38 centers in the United States. It compared memantine with placebo in patients with moderate to severe Alzheimer's disease who were also being treated with a stable dose of donepezil.

Subjects enrolled in this study met NINCDS-ADRDA diagnostic criteria for AD and had baseline Mini Mental Status Examination (MMSE) scores of 5-14 and received donepezil treatment for at least six months, with a stable dose for at least three months.

Subjects were randomized to receive either memantine 10mg bid or placebo for 24 weeks, preceded by a 2-week single blind placebo treatment. The first four weeks of double-blind treatment consisted of a titration of 5mg/wk to achieve 10mg bid by week 4 (similar to the titration scheme for study 9605)

The primary efficacy measures were the modified ADCS-ADL and the SIB. The primary analyses were carried out on the ITT population on the change from baseline to week 24 measurements using an LOCF approach to impute missing data. An ANCOVA using treatment and center as main effects and baseline score as the covariate was used for the analyses of least square means.

The study enrolled 404 subjects, of which 203 received memantine and 201 received placebo. Actual baseline MMSE scores ranged 5-16. A total of 322 completed the study (172 on memantine, and 150 on placebo).

The results of the primary analyses are shown in Table 3 (taken from Dr. Mani's review, page 23).

Table 3: Study MD02 – Primary Analyses

Least Square Mean Change From Baseline In ADCS-ADL

	Placebo/Donepezil		Memantine/Donepezil		p-value
	N	Mean	N	Mean	
Week 24 (LOCF)	197	-3.4	198	-2.0	0.028
Week 24 (OC)	152	-3.3	172	-1.7	0.020

Least Square Mean Change From Baseline In Severe Impairment Battery

	Placebo/Donepezil		Memantine/Donepezil		p-value
	N	Mean	N	Mean	
Week 24 (LOCF)	196	-2.5	198	0.9	< 0.001
Week 24 (OC)	153	-2.4	171	1.0	< 0.001

The between group difference in the mean modified ADCS-ADL score was small (1.4) but statistically significant in favor of memantine (p=0.028). The between group difference in the mean SIB scores was 3.4 points in favor of memantine. This was highly statistically significant (p<0.001). In this study, the SIB improved slightly (1 point) in the memantine-treated patients at week 24, whereas placebo-treated patients continued to deteriorate.

Dr. Massie verified the sponsor's analyses but notes that the p-values were based on an ANCOVA model, which relies on a normal distribution of the data. However, the assumption of normality was violated. The protocol did not specify an alternate non-parametric test in this case. Dr. Massie performed two non-parametric analyses and the p-values nonetheless remained significant for both primary measures.

The Division requested inspection of one center in this study based on the observation that this center included efficacy outliers such that exclusion of this center would result in a non-significant p-value for the ADCS-ADL.

The investigator of the center in question was Dr. Heiser. This center enrolled and randomized 11 subjects, of which 9 completed the study. DSI inspected all the efficacy data and discovered a discrepancy in 2 subjects (both on placebo) regarding the data recorded in the case report form and in the sponsor's dataset. In both cases, a positive value for the ADCS-ADL and SIB in the CRF appeared as a "zero" in the data listing. Although such an error could have incorrectly lowered the mean placebo scores for these measurements, our statisticians Dr. Massie and Dr. Jin assure us that we used the correct scores in our analyses and confirmed the sponsor's analyses (suggesting that the sponsor used the correct values as well). This does not appear to be an issue that affects the results.

In summary, this study also supports the efficacy of memantine in moderate-severe dementia of the Alzheimer's type by virtue of positive results on a cognitive scale, the SIB, and a functional scale, the modified ADCS-ADL.

Dr. Massie conducted a subgroup analysis by baseline MMSE scores (<10, ≥10). It shows that subjects with baseline MMSE scores <10 did exhibit treatment effects that favored

drug for both the ADL and the SIB (although it did not reach nominal significance for the ADL, it seems more likely related to a power issue).

Table 4: MEM-MD-02 - Mean Outcome Measures (LOCF) by MMSE and Treatment

Variable	Group	Treatment Code	n	Baseline	Endpoint</thead><tbody>	Treatment Effect p value *
Primary						
ADL	< 10	Placebo	72	32.4 (9.3)	-4.6 (6.1)	0.1682
	< 10	Memantine	89	33 (10.7)	-2.8 (7.6)	
	>= 10	Placebo	125	38.5 (8.5)	-2.4 (5.9)	0.0821
	>= 10	Memantine	109	37.9 (8.4)	-1.1 (5.3)	
SIB	< 10	Placebo	72	69.1 (14.5)	-6.2 (9.9)	0.0023
	< 10	Memantine	89	67.4 (15.4)	0.1 (9.8)	
	>= 10	Placebo	124	86 (9.3)	0.0 (7.6)	0.0450
	>= 10	Memantine	109	86 (9.7)	1.8 (6.0)	
Secondary						
CIBIC+	< 10	Placebo	72	N/A	4.90 (1.10)	0.0353
	< 10	Memantine	89	N/A	4.67 (1.03)	
	>= 10	Placebo	124	N/A	4.52 (0.99)	0.1209
	>= 10	Memantine	109	N/A	4.19 (1.01)	

* based on ANCOVA model containing effects for Treatment, Center, and Baseline Score

Study 9403

9403 was a randomized, double-blind, placebo-controlled parallel arm study conducted at 7 centers in Latvia. It compared memantine with placebo in a heterogeneous population consisting of subjects with moderate to severe dementia due to a variety of conditions including Alzheimer's disease, vascular disease, and mixed dementia. The protocol did not specify the criteria for making these diagnoses at study entry.

Subjects were randomized to receive either memantine 10mg once daily (starting at 5mg daily for one week) or placebo for 12 weeks.

The primary efficacy measures were the Behavioral Rating Scale in Geriatric Patients (BGP) Care Dependency Subscale, and the Clinician Global Impression of Change (CGI-C), a global measure (a 7-point scale which was dichotomized for a responder analysis).

A third primary measure was introduced in a second analysis plan which was formulated *post-hoc* several years after the blind was broken and the study results published.[1] This was the BGP Cognitive Subscale, which was a subset of the BGP Care Dependency Subscale. As I described previously in this memo, it contains 5 items relating to cognition out of the 23-item BGP Care Dependency Subscale. In this post-hoc analysis plan, the 7-

[1] The study was completed in 1995 and the results published in J Geriatr Psych in 1999. The sponsor finalized the post-hoc analysis plan on May 24, 2002.

point CGI-C was designated as a primary analysis measure instead of the dichotomized scale as originally conducted.

In the original analysis plan, the primary analysis included the ITT population using the worst possible score (worst change) to impute missing data. The BGP Care Dependency Subscale change from baseline to endpoint was analyzed using the Wilcoxon-Mann-Whitney U tests. The Fisher's exact test was planned for the CGI-C dichotomized scale at endpoint (*i.e*, a responder analysis, although the protocol did not clearly define a "responder").

In the post-hoc analysis plan, all three primary measures were analyzed using the Wilcoxon rank-sum test, stratified by center. This plan used an LOCF approach to impute missing data, rather than the "worst case" approach used originally.

In total, 166 subjects were enrolled in the study: 82 on memantine and 84 on placebo. Of these, 158 completed the study: 78 on memantine and 80 on placebo. The treatment groups were largely comparable at baseline.

Using the dichotomized CGI-C, 73% of memantine-treated patients and 45% of placebo-treated patients were considered responders ($p<0.001$). The between group difference in mean BGP Care Dependency Subscale score was 1.9 in favor of memantine ($p=0.016$).

The post-hoc analysis results are shown in Table 5 (taken from Dr. Mani's review, page 22).

Table 5: Study 9403 – Post-Hoc Primary Efficacy Analyses

	LOCF Analysis			OC Analysis		
	Memantine (n = 82)	Placebo (n = 84)	p-value*	Memantine (n = 78)	Placebo (n = 80)	p-value*
CGI-C	3.09	3.52	0.001	3.01	3.48	0.001
BGP Care Dependency	-5.29	-3.27	0.012	-5.56	-3.50	0.010
BGP Cognitive	-1.85	-1.12	0.001	-1.95	-1.19	0.001

*p-values are based on Cochran-Mantel-Haenszel test for row means (using modified ridit score) controlling for center

The between group difference in mean CGI-C score using the 7-point scale was 0.4 and in favor of memantine ($p=0.001$). The between group difference in the change from baseline BGP Care Dependency Subscale Score was 2.0 and in favor of memantine (0.012). The between group difference in the change from baseline BGP Cognitive Subscale score was 0.8 and in favor of memantine ($p=0.001$).

After enrollment, subjects were considered to have dementia of the Alzheimer's type if their score on the modified Hachinski Scale at study entry was ≤ 4. Using this criteria, 79 subjects (41 on memantine and 38 on placebo) were so identified. Of these, 76 completed the study (39 on memantine, 37 on placebo). It is notable that randomization was not stratified according to dementia subgroup.

The post-hoc analysis in this subgroup showed:

Between group difference in mean CGI-C score (7-point scale) at endpoint was 0.4 in favor of memantine (p=0.003)

Between group difference in mean change from baseline BGP Care Dependency Subscale score was 3.0 in favor of memantine (p=0.003)

Between group difference in mean change from baseline in BGP Cognitive Subscale score as 1.0 in favor of memantine (p-0.007).

As Dr. Mani points out, this study does not provide convincing evidence of memantine's efficacy in moderate to severe Alzheimer's Disease because of the following design and analysis issues:

- The heterogeneous nature of the study population: Alzheimer's Disease, Vascular Dementia, or mixed dementia.
- 48% did not undergo brain imaging of any kind. Brain imaging is a standard screening procedure to exclude other causes of dementia.
- The identification of the subset of AD patients was made *post-hoc*, using a method of diagnosis of AD that deviates from the now widely accepted method (*i.e*, the Hachinski scale was used, vs. the NINDS-ADRDA criteria). The post-hoc nature means randomization was not stratified by dementia type.
- The study lacked a satisfactory prospectively designated cognitive measure.
- The post-hoc nature of the analysis on cognition, using a cognitive scale of questionable utility: the BGP Cognitive subscale

Safety

The safety data come from eight phase 2/3 controlled trials in various forms of dementia (including vascular and AD), four open label extensions of these trials, and two phase 2/3 controlled trials in neuropathic pain, 30 clinical pharmacology trials, and limited safety data from ongoing trials exploring other indications, as well as post-marketing safety reports.

The safety database includes data on 487 subjects exposed to memantine in clinical pharmacology trials and 1,748 subjects exposed to memantine in dementia and neuropathic pain trials ("Group 1" in Dr. Boehm's review; the primary safety database for which complete safety data exist. I generally limit my safety discussion to this group, unless otherwise stated). The exposures exceed ICH guidelines, although not all of the exposures were in subjects with AD (27% of the 1,748 subjects had AD). The sponsor reports that over 4,000 subjects have been exposed in completed trials exploring other indications and in ongoing trials, and estimates over 400,000 person-years of post-marketing experience. There were 862 subjects that were exposed for $\geq$ 24 weeks (32% with AD), and 277 that were exposed for $\geq$ 52 weeks (17% with AD).

The percentage of deaths and serious adverse events (SAE's) were similar across memantine and placebo treatment groups and the causes of death were typical of those expected in an elderly population. Mortality risk in the controlled dementia studies was

2% and was similar between memantine and placebo-treated subjects. There were no worrisome clustering of unexpected SAE's in memantine-treated subjects. There were three reported cases of pancreatitis, with two having coexisting cholelithiasis. About 10% dropped out due to adverse events, and this was similar between memantine and placebo-treated subjects. Adverse events were generally infrequent. In the dementia controlled trials, no adverse event occurred with greater than 7% incidence in the memantine group. The most commonly reported adverse events occurring more frequently in memantine-treated subjects included dizziness, headache, constipation, pain, and dyspnea.. Post-marketing reports include epidermal necrolysis (2), aplastic anemia (1) and liver failure (1). One advantage of memantine over currently approved cholinesterase inhibitors is the apparent lack of gastrointestinal symptoms (nausea, vomiting) associated with the latter.

Memantine does not appear to be associated with changes in blood pressure or pulse, but insufficient data were available to adequately assess effects on orthostatic blood pressure changes. There is no evidence of significant effects on the ECG (including no evidence for QT prolongation); however, as Dr. Boehm points out, ECG's were not adequately examined in certain trials. He recommends that the sponsor reanalyze all ECG interval data after they have been systematically read by a central laboratory using standard measuring methodology, although not as a requisite for approval.

There was evidence for elevated alkaline phosphatase levels in controlled dementia trials (but not in the neuropathic pain trials), but the mean elevation was small (+7 points, compared to no change in the placebo group). The elevation in mean alkaline phosphatase levels were largely driven by 5 outliers in the memantine group. Dr. Boehm reviewed all five cases and none appeared to be related to memantine use (page 43 of his review). There was no evidence for hepatic transaminase or bilirubin elevations.

Overall, memantine appears to be reasonably safe for use at the recommended marketing dose of 10mg bid.

Conclusion

The sponsor has submitted efficacy data from three randomized, controlled studies. Two of these studies (9605 and MD02) provide evidence to support the efficacy of memantine in the treatment of moderate to severe dementia of the Alzheimer's type by virtue of the fact the both are positive using a cognitive scale and a functional scale (SIB and modified ADCS-ADL in both). Although the SIB was a secondary outcome measure in study 9605, the robustness of the finding persists even if one were to correct for multiple secondary efficacy comparisons. Since this is the first drug to be approved for the subgroup of severely demented patients (at least as defined by the MMSE), we explored the evidence of efficacy in this subgroup. In both studies, the effect on cognition, as measured by the SIB, was nominally significant. However, nominal significance was not evident in either study using the primary global or functional measures (although the treatment effect on the ADL in severely demented patients in MD02 was numerically about the same as in the moderate group). Nonetheless, these studies were not designed to demonstrate efficacy in this subgroup, *per se*, and I believe the findings are supportive of its use in this sub-population.

The third study, 9403, I do not believe can be considered supportive due to a myriad of design and analysis issues. Despite these positive findings in two studies, certain issues warranted discussion in front of an advisory committee because we had questions regarding the population studied, the study designs and endpoints used.

The application was presented to the Peripheral and Central Nervous System Advisory Committee on Wednesday, September 24, 2003. The committee voted unanimously that the population was adequately identified and studied (at least in the two U.S. studies), and that the study designs and endpoints that were used were adequate to establish efficacy. They felt, again unanimously, that sufficient evidence of efficacy and safety had been presented, although the treatment effect appears to be quite modest.

Taking all of these issues into consideration, I believe adequate safety and efficacy information has been presented to support approval of memantine for use in moderate to severe dementia of the Alzheimer's type at a dose of 10 mg bid.

/S/

Armando Oliva, M.D.
Neurology Team Leader

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/s/

Armando Oliva
10/2/03 04:23:43 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: September 17, 2003

To: Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products (HFD-120)

Through: Deborah B. Leiderman, M.D., Director /S/
Michael Klein, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

From: Katherine Bonson, Ph.D., Pharmacologist /S/
Controlled Substance Staff (HFD-009)

Subject: NDA review of abuse potential
NDA 21-487
Memantine
Treatment for moderate to severe dementia
Sponsor: Forest Laboratories, Inc.

Background:

This consult is an NDA review of the abuse potential of memantine. Memantine is a NMDA receptor-channel complex antagonist, which acts by blocking the same site as the dissociative anesthetics phencyclidine (PCP) and ketamine, and the antitussive dextromethorphan. Memantine has been marketed in Germany since 1982 for the treatment of dementia, Parkinson's Disease, and dystonias and is currently approved for the treatment of moderately severe Alzheimer's Disease in the European Union.

CSS requested and received an outside consultation on the abuse potential of memantine from a Special Government Employee, Dr. Harriet de Wit, Associate Professor in the Department of Pharmacology at the University of Chicago and an expert on drugs of abuse. In her consult to CSS, Dr. de Wit evaluated the published medical and scientific literature for clinical and preclinical studies as of July 2003.

Conclusions:

* European epidemiological databases do not show any evidence for abuse, dependence or addiction related to memantine, despite its availability in Germany since 1982.

* Sponsor-submitted studies show that high dose memantine produced slowed motion and ataxia. No monkey (out of 4 monkeys) self-administered memantine above placebo levels, an effect that was not altered by a 4 week period of forced administration of memantine. Only 1 of 4 monkeys showed withdrawal signs (decreased food intake, muscle rigidity and increased aggression) during discontinuation from forcible administration of memantine. No monkey self-administered memantine during the discontinuation phase.

* Published reports show that memantine, PCP and ketamine fully generalize to the MK-801 cue in drug discrimination studies with rats and monkeys, while dextromethorphan produces partial generalization. Memantine is self-administered by monkeys, but at a rate less than that for PCP.

* Memantine shows significant binding to only one site in the brain, the MK-801 site (the NMDA receptor in the channel). The Ki of memantine in rat brain is higher than that of PCP, but is lower than that of ketamine (Bresink et al., 1995).

Recommendation:

* CSS recommends that the Drug Abuse and Dependence section of the memantine label read as follows:

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Memantine HCl is not a controlled substance.

Physical and Psychological Dependence: Memantine HCl is a low to moderate affinity noncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon drug discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post-marketing experience outside the U.S. has provided no evidence of drug abuse or dependence. However, these abuse liability data were not collected systematically.

APPENDIX

I. Summary of Data Related to Abuse Potential from Preclinical Studies:

A. Biochemical Pharmacology (in vitro)

Memantine was tested at a full range of neurotransmitter sites to assess binding affinity. There was relatively high affinity for only one site in the brain: the NMDA receptor-channel complex. Binding affinity for the NMDA channel site for PCP, memantine and ketamine is shown below (Bresink et al., 1995):

	cortex	cerebellum	striatum
PCP	42.2 nM	180 nM	n/d
memantine	690 nM	700 nM	433 nM
ketamine	1,190 nM	2,307 nM	n/d

B. Behavioral Pharmacology

The Sponsor submitted a behavioral study in rhesus monkeys following memantine administration ("A study of SUN-Y7017 in rhesus monkeys by gross behavioral observation for acute CNS effects and intravenous self-administration"). Two of 2 monkeys showed increased aggression at 1 mg/kg memantine (i.v.) and increased grimacing at 2 mg/kg (i.v.). At 4 mg/kg (i.v.), both animals showed slowed motion and ataxia. All behaviors resolved within 24 hrs. In a self-administration study, no monkeys (out of 4 monkeys) self-administered memantine above placebo levels when offered at doses of 0.06, 0.125 and 0.25 mg/kg/infusion (i.v.). Animals were then forcibly administered memantine at 1 mg/kg/infusion (i.v.) for four weeks, during which time they were given the opportunity to self-administer memantine. None of the four monkeys self-administered memantine during the forcible administration phase. During a 3-day withdrawal period following discontinuation of forcible memantine administration, only 1 of 4 monkeys showed withdrawal signs (decreased food intake, muscle rigidity and increased aggression). No monkey self-administered memantine during the discontinuation phase.

The de Wit consult states the following regarding preclinical behavioral pharmacology:

"The behavioral effects of memantine resemble low doses of PCP in preclinical models (Dimpfel et al 1987)... Several drug discrimination studies with rats have examined generalization to memantine in PCP-trained rats (Sanger et al, 1992; Sanger, 1992; Zajaczkowski et al, 1996, Nicholson et al, 1998). In these studies there was generalization to the PCP lever, although in the Nicholson et al (1998) study this occurred

... at doses that decreased rates of responding. [Rats trained to discriminate MK-801 showed full generalization to memantine, PCP, ketamine and MK-801, but only partial generalization to dextromethorphan (Grant et al, 1996).] Monkeys (N=4) trained to discriminate PCP from saline showed generalization to memantine (Nicholson et al, 1998). [Dextromethorphan produced dose-dependent generalization to PCP in rats, but a mixed response in monkeys (2 full generalization, 1 partial generalization) (Nicholson et al., 1999).]

"In the arguably more relevant tests of self-administration, Nicholson et al (1998) reported that 4 out of 4 monkeys tested self-administered memantine at rates higher than placebo, although their maximal rates of responding were substantially lower than the rates of responding for PCP (only 25% to 50% of PCP rates)." [Dextromethorphan was self-administered in 5 of 6 monkeys following training with PCP (Nicholson et al., 1999).]

II. Summary of Data Related to Abuse Potential from Clinical Studies:

Drugs that act as NMDA channel blockers are known to produce hallucinations, which are sometimes sought by drug abusers. This response was reported as an adverse event by patients who participated in the clinical trials.

When patients participating in all placebo-controlled dementia studies with memantine at any dose are summed, a total of 24 of 940 patients (2.6%) reported hallucinations. This is more than the rate reported by placebo-treated patients (15 of 922 patients (1.6%)). When these patients are separated by type of dementia, Alzheimer's dementia patients reported hallucinations at a rate of 4.0% (16 of 396 patients) compared to 10 of 394 placebo patients (2.5%) while vascular dementia patients reported hallucinations at a rate of 1.5% (8 of 544 patients) compared to 5 of 528 placebo patients (0.9%). It is not possible to determine to what degree the disease process of dementia contributes to the hallucinatory response to memantine.

III. Summary of Data from Clinical Abuse Potential Studies:

The de Wit consult states the following about clinical abuse potential studies:

"Unfortunately, few controlled studies have been conducted to assess the abuse [potential] of NMDA antagonists, and there is little systematic data using these drugs in humans. Further, the standardized subjective effect measures that are sensitive to other classes of drugs may not be sensitive to the unique effects of this class of drugs. Thus, there is no "gold standard" of a similar drug to serve as an appropriate comparison drug for a new NMDA such as memantine, making it difficult to design an appropriate abuse [potential] study.

"Memantine has been administered to human volunteers in several studies designed for other purposes (Hart et al, 2002; Bisaga et al, 2001; Collins et al, 1998). Collins et al (1998) tested memantine as a potential pharmacotherapy for cocaine use. They administered memantine (20 mg) for 7-10 days before laboratory sessions involving administration of cocaine, in 8 cocaine abusers. Memantine increased ratings of "high" and "feel a good drug effect" [following cocaine administration], and how much they would pay after all three doses of cocaine (12, 25 and 50 mg)... These findings are consistent with what would be expected with a drug with abuse potential, but provide at best indirect evidence.

"In one unpublished study (Bisaga et al, 1998), opiate addicts received doses of memantine up to 60 mg (3 times higher than the usual therapeutic dose), with no apparent side effects or evidence of abuse potential. In a human drug discrimination study using 6 subjects with some stimulant use histories (Hart et al, 2002), memantine (40 mg) [did not generalize to] methamphetamine. [However,] memantine (40 mg) produced ... increased ratings of good drug effect and drug liking [associated with methamphetamine administration], and a moderately high street value compared to placebo. Ratings of drug liking and street value after memantine [reached equivalent levels to those produced by] 5 to 10 mg methamphetamine. These studies were not specifically designed to assess the abuse [potential] of memantine, and the conclusions that can be drawn about abuse [potential] are limited by the doses that were included for testing" [as well as the low statistical power].

IV. Summary of Epidemiological Data Related to Abuse Potential

IMS data submitted by the Sponsor show that the following number of prescriptions were written for memantine in Germany in the years 1999-2002:

2002	—
2001	—
2000	—
1999	—

The de Wit consult states that, "Memantine has been available clinically in Europe for the past 15 years, and has been prescribed to over 200,000 patients without apparent problems (Parson et al., 1999). The absence of reports of abuse or misuse in Europe suggests that it has low abuse potential [if any]. However, this conclusion is limited by the unknown sensitivity of the drug abuse detection and monitoring systems in Europe, and by the possibility that drug users in Europe prefer different drugs than U.S. users."

The Sponsor submitted a review of four European epidemiological databases related to the abuse potential of memantine, three that track spontaneous reports and one that conducted a formal drug abuse surveillance program:

World Health Organization Centre for Drug Monitoring (Uppsala, Sweden)
There were 27 adverse drug reaction case reports related to memantine in the WHO database, which represents 70 countries. No dates were given for the reporting period. None of these reported symptoms were indicative of abuse potential. There were two cases of "psychosis", but one of the patients was concomitantly receiving haloperidol for a diagnosis of psychosis.

Bundesinstitut fur Arzneimittel und Medizinproducte (BfARM)
The BfARM is the German counterpart to the FDA. This database of spontaneous adverse drug reactions, similar to the Medwatch program, had 41 case reports related to memantine. No dates were given for the reporting period. None of these reported symptoms were indicative of abuse potential. There appears to be overlap between the WHO database and the BfARM database, given that both report two cases of psychosis, with one of the patients concomitantly treated with haloperidol.

Merz Pharmaceuticals GmbH Database
This pharmaceutical company certified that two decades of post-marketing surveillance data for memantine showed no case reports suggestive of abuse potential. Specifically, the company has not received any spontaneous reports of withdrawal symptoms following discontinuation of memantine, and there have not been any reports of symptoms indicative of abuse of the drug.

Institut fur Therapieforschung (ITF; Munich, Germany)
The EBIS-Med surveillance program, run by ITF, actively collects data on the abuse of medications from drug abuse treatment centers in Germany. Memantine was not mentioned in the 2001 EBIS-Med report for the years 1995-2000, nor in the 1997 EBIS-Med report for the years 1988-1997. The Sponsor notes in the narrative that the database is sensitive to emerging drugs of abuse as well as drugs without known abuse in that it has cited instances of abuse for tramadol, dextromethorphan (an NMDA antagonist) as well as antidepressants.

V. Labeling

The Sponsor has proposed the following wording for the Drug Abuse and Dependence section of the label:

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Memantine HCl is not a controlled substance.

Physical and Psychological Dependence:

C

J

[

]

The data submitted in the Integrated Summary of Safety for this NDA do not support the wording proposed by the Sponsor for the Drug Abuse and Dependence section. Hallucinations were reported in clinical trials at rates above those of placebo, although statistical significance was not established.

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Zajaczkowski W, Moryl E, Papp M (1996) Discriminative stimulus effects of the NMDA receptor antagonists MK-801 and CGP37849 in rats. Pharmacol Biochem Behav 55:163-168

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Katherine Bonson
9/25/03 09:59:38 AM
PHARMACOLOGIST

Michael Klein
9/29/03 09:13:37 AM
CHEMIST

Deborah Leiderman
9/30/03 03:38:58 PM
MEDICAL OFFICER

MEMORANDUM OF MEETING MINUTES

Meeting Date: January 25, 2001 **Time:** 1:30 pm **Location:** Rm. 4023

Application: IND 33,392/Memantine
Indication: Alzheimer's Disease
Type of Meeting: Pre-NDA Meeting
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Melina Fanari, R.Ph.

FDA Attendees:
Russell Katz, M.D., Division Director
Ranjit Mani, M.D., Medical Reviewer
Maryla Guzewska, Ph.D., CMC TL
Kun Jin, Ph.D., Biometrics Team Leader
Ramana Uppoor, Ph.D., Biopharm TL
Melina Fanari, R.Ph., Regulatory Management
Armando Oliva, M.D., Team Leader
Barry Rosloff, Ph.D., Pharmacology TL
Janusz Rzeszotarski, Ph.D., CMC
Kallappa Koti Ph.D., Biometrics
Maria Sunzel, Ph.D., Biopharm

Sponsor Attendees:
Im Abramowitz, Human PK
Sebastian Assenza, CMC
Theresa Fico, Pharm/Tox
Ivan Gergel, Medical
Charles Lindamood
Paul Tiseo, CNs Medical
Hans-Joerg Moebius, R&D Pharma
Albrecht Stoeffler, CNS Medical
Robert Ashworth, Reg Affairs
Monica Fencik, Project Management
Charles Flicker, CNS medical
Lester Gibbs, Reg Affairs
Lawrence Olanoff, Scientific Affairs
Jane Wu, Biostatistics
Guenter Quack, Pharm/tox

Discussion Points:

The following is a list of the sponsor's proposed questions with the appropriate FDA response:

Question 1: Forest proposes to conduct the stability of the 5, 10 and 20 mg product under current ICH conditions using the matrix protocol designs illustrated in Table 2-2 and Table 2-3. The matrix stability protocol incorporates 3 —— bottles and 1 blister package. Does the agency agree to this proposal? **Yes**

Question 2: The NDA will contain at least 3 months of stability data at the time of submission. Forest proposes to submit 3 month stability data for the 5,10 and 20 mg products manufactured in —— and supplement the submission with at least —— data at the time of approval. Does the agency agree with this proposal?

No, there is insufficient data for this formulation. ICH guideline should be reviewed to determine what stability data are required.

Question 3: A complete battery of nonclinical studies has been completed for memantine, including pharmacology, drug disposition, mutagenicity, carcinogenicity, and actue, repeated-dose, and reproduction/developmental toxicity studies. The studies indicate that, as expected, the central nervous system is the primary target organ for toxicity. Memantine is not anticipated to be mutagenic, carcinogenic, or a reproductive/ developmental hazard under conditions of therapeutic dosage regimens.

Vacuolization and necrosis of neurons in the retrosplenial and cingulate cortex were observed in rodents, and corneal epthelial lesions in mice, rats, and dogs. For both observations, safety margins are adequate, and investigative toxicity studies suggest mechanisms not relevant to proposed clinical dosing regimens.

Does the Division agree that no additional preclinical studies are required for NDA filing?
Information on comparative drug metabolic patterns (between animals and humans) should be submitted. Also food consumption data in the carcinogenicity studies should be expressed as grams of food consumed per animal. No additional animal studies are anticipated at this time.

Question 4: For the preclinical studies, Forest would like to confirm that the only electronic dataset required is the individual animal line listings of the tumor data from the carcinogenicity studies as specified on page 61 of the electronic submissions guideline (Providing Regulatory Submissions in Electronic Format — NDAs, January1999).

Is this proposal acceptable to the FDA? **Yes**

Question 5: Memantine has been extensively studied in humans. Forest proposes that there is sufficient data on human pharmacokinetics and bioavailability for the approval and labeling of memantine. Does the Division agree?

A full characterization of the metabolism of memantine in humans, and its effects on CYP450 isoenzymes would be needed to be part of an NDA. In addition, information about drug-drug interactions, especially with concomitant medications in the targeted population, is needed. Information of the food effects on the immediate release formulation will also be needed.

Question 6: In pivotal Phase III studies, two different tablet formulations were used A formulation was used in Studies 9605 (US) and 9408 (France) while a formulation was used in Study 9403 (Europe). Study 9202 (UK) used both formulations. Forest intends to manufacture and market the formulation. All tablet strengths will use the same formulation (drug to excipient ratio) but with different colors for film coating. Since the drug is highly soluble and highly permeable (completely absorbed), we are requesting a waiver for an in vivo bioequivalence study for this product. We will have in vitro dissolution data to support the bioequivalency of the formulation manufactured by Forest to the tablets manufactured by Merz. Does the Division agree?

Question 7: Based on the data presented in this document, Forest believes that memantine can be classified according to the Biopharmaceutics Classification System

(BCS) as Class 1 and that in vivo bioequivalence studies will be waived. Does the Division agree?

Additional information is needed with respect to questions 6 & 7, therefore a separate teleconference will be held. A separate letter providing detailed comments will be sent to the sponsor.

Question 8: Are the efficacy data presented here adequate to support an application for the use of memantine in the

T

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• The Division might be willing to consider a claim for the efficacy for Alzheimer's Disease based on Study 9605, and a further randomized, controlled study that studied the entire spectrum of severity of that disease.

• If the sponsor intends to pursue a claim, in a formal NDA for memantine, that is solely [redacted] Alzheimer's Disease, the Division plans to discuss that claim at a PCNS Advisory Committee meeting.

• The sponsor plans a formal study to evaluate the efficacy of the proposed controlled-release formulation of memantine.

Question 9: Forest believes that the existing safety database involving studies in dementia and multiple other indications is substantial. Does the Division agree that this will be adequate?

•The sponsor does appear to have an adequate safety database to support an NDA for memantine. It was conveyed to the sponsor that, if an NDA for memantine is submitted, the ICH guidelines (for exposure) will need to be met for patients with Alzheimer's Disease at the dose being proposed for use.

ABUSE POTENTIAL

• Since memantine is a putative NMDA antagonist its abuse potential might need further characterization.

• The sponsor stated that studies to characterize its abuse potential had already been done in 2 animal species, and that a submission summarizing these studies would be made available in the near future to this Division for consultation to the Controlled Substances Staff who would help determine if more studies were needed.

/s/

Russell Katz
3/7/01 11:31:04 AM

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: March 3, 2003	DESIRED COMPLETION DATE: May 5, 2003 PDUFA DATE: Oct. 20, 2003	ODS CONSULT #: 03-0094

TO: Russell Katz, MD
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Melina Griffis
Project Manager
HFD-120

PRODUCT NAME: [redacted] Primary name) **Namenda** (Alternate name) (Memantine Hydrochloride Tablets) 5 mg, 10 mg, 15 mg, and 20 mg **NDA #'s: 21-487 and 21-627**	**SPONSOR:** Forest Laboratories, Inc.

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120) for a review of the proposed proprietary names '[redacted]' and "Namenda" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proposed name, [redacted] However, DMETS has no objections to the use of the proposed name "Namenda". DMETS considers this a final review. If the approval of the application is delayed beyond 90 days from the signature date of this review, the name must be re-evaluated. A re-review of the name and its associated labels and labeling prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

2. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review.

3. DDMAC finds the names '[redacted]' and "Namenda" acceptable from a promotional perspective.

/S/

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 15, 2003

NDA NUMBERS: 21-487 and 21-627

NAME OF DRUG: —— (Primary name) and **Namenda** (Alternate name)
(Memantine Hydrochloride Tablets)
5 mg, 10 mg, 15 mg, and 20 mg

NDA SPONSOR: Forest Laboratories, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products, for an assessment of the proprietary names "——" and "Namenda" regarding potential name confusion with other proprietary and/or established drug names. The draft blister container labels, carton and draft package insert labeling for —— and Namenda were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

—— Namenda is the proposed proprietary name for memantine hydrochloride, an orally active N-methyl-D-aspartate (NMDA) receptor antagonist, indicated for the treatment of moderate to severe dementia of the Alzheimer's type. The recommended starting dose of —— Namenda is 5 mg once daily. The recommended target dose is 20 mg per day. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day). The minimum recommended interval between dose increases is one week. —— Namenda will be available as a tablet in strengths of 5 mg, 10 mg, 15 mg, and 20 mg

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[i,ii] as well as several FDA databases[iii] for existing drug names which sound-alike or look-alike to —— and Namenda to a degree where potential confusion between drug names

[i] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[ii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[iii] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[iv] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[v] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies for each proposed name, consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names, —— and Namenda. Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified three medication names that have potential for confusion with —— These names include Norvasc, Nuvaring and Avita. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage. The Expert Panel did not identify any names that were thought to have potential confusion with the proposed name, Namenda.

2. DDMAC did not have any concerns with —— or Namenda with regard to promotional claims.

[iv] WWW location http://www.uspto.gov.——

[v] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
— or Namenda	Memantine Hydrochloride Tablets: 5 mg, 10 mg, 15 mg, and 20 mg	The recommended starting dose of — 5 mg once daily. The recommended target dose is 20 mg per day. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day). The minimum recommended interval between dose increases is one week.	
Nuvaring (Rx)	Etonogestral and Ethinyl Estradiol Vaginal Ring 11.7 mg/2.7 mg	Insert one ring vaginally, prior to or on day five of cycle. Leave ring in place for three weeks, then remove for one ring-free week; repeat.	**S/A, L/A
Avita (Rx)	Tretinoin Cream; Gel 0.025%	Apply sparingly to cleansed and completely dry skin once daily at bedtime.	**S/A
Norvasc (Rx)	Amlodipine Tablets 2.5 mg, 5 mg, and 10 mg	Hypertension: 5 mg once daily, to a maximum dose of 10 mg once daily. Angina: 5 mg to 10 mg daily, using lower dose for elderly and patients with hepatic insufficiency.	**L/A

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Six separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of — and Namenda with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 105 health care professionals (pharmacists, physicians, and nurses) for each name. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for — and Namenda (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 15mg 1 po qd #30	15 mg, take one by mouth daily, dispense #30.
Inpatient RX: 15mg po QD	

Namenda

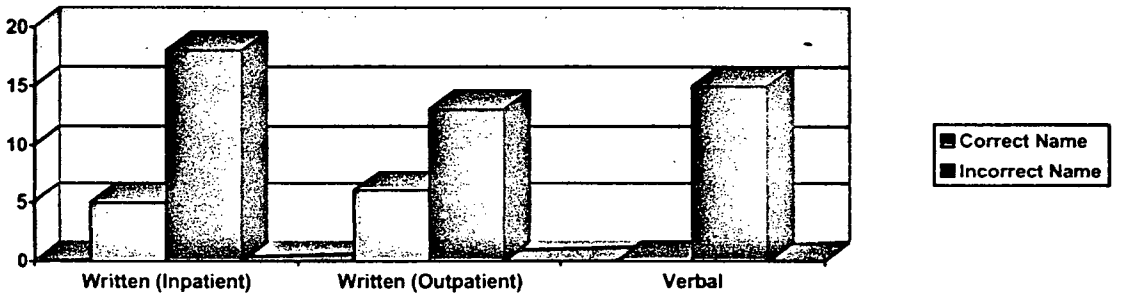
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Namenda 20mg Sig: 1 po QD #30	Namenda 20 mg, take one by mouth daily.
Inpatient RX: Namenda 20mg po QD	

2. Results:

i. The results for —— are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	39	23 (59%)	5 (22%)	18 (78%)
Written Outpatient	35	19 (54%)	6 (32%)	13 (68%)
Verbal	31	15 (48%)	0 (0%)	15 (100%)
Total	105	57 (54%)	11(19%)	46 (81%)



Among the verbal prescription study participants for . . . — 100% of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of — ". The incorrect responses were .

'l), *ı (l).* None of the interpretations are similar to a marketed drug product.

Among the written inpatient prescription study participants for — 18 of 23 (78%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of The incorrect responses were .

None of the interpretations are similar to a marketed drug product.

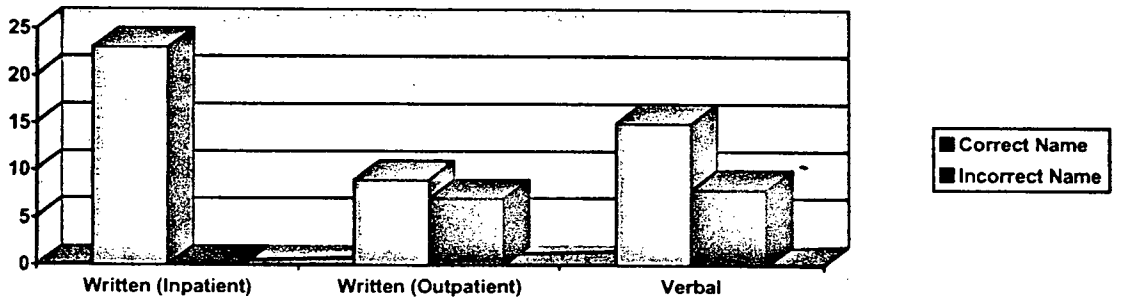
Among the written outpatient prescription study participants for — , 13 of 19 (68%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of ' — . The incorrect responses were .

'e (11). None of the interpretations are similar to a marketed drug product.

ii. The results for **Namenda** are summarized in Table 3.

Table 3

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	35	23 (66%)	23 (100%)	0 (0%)
Written Outpatient	31	16 (52%)	9 (56%)	7 (44%)
Verbal	39	23 (59%)	15 (65%)	8 (35%)
Total	105	62 (59%)	47 (76%)	15 (24%)



Among the verbal prescription study participants for Namenda, 8 of 23 (35%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Namenda". The incorrect responses were *Namedna (1), Naminda (6), and Naminemda (1).* None of the interpretations are similar to a marketed drug product.

Among the written inpatient prescription study participants for Namenda, none of the participants interpreted the name incorrectly.

Among the written outpatient prescription study participants for Namenda, 7 of 16 (44%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Namenda". The incorrect responses were *Mamenda (1), Namends (1), Namerda (1), Naminda (3), and Navenda (1).* None of the interpretations are similar to a marketed drug product

C. SAFETY EVALUATOR RISK ASSESSMENT

1. —

In reviewing the proprietary name — ", the primary concerns raised were related to three look-alike and/or sound-alike names. The products considered to have potential for name confusion with — were: Nuvaring, Avita, and Norvasc.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between — and Nuvaring, Avita or Norvasc. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed

name, [redacted] However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size.

a. Norvasc has look-alike similarities to the proposed name, [redacted] Norvasc contains amlodipine

and is indicated for the treatment of hypertension and angina. The recommended dose of Norvasc is 5 mg to 10 mg daily. Both names contain seven letters, and the prefix of each name differs by one letter [redacted] The ending of each name is distinguishable when written mainly to due to the upstroke of the letter [redacted] However, if the upstroke of the letter " is not prominent, the suffixes may look similar. Both drugs also share an overlapping route of administration (oral), dosage form (tablet), strengths (5 mg and 10 mg), and dosing regimen (once daily). Additionally, Norvasc and [redacted] will be stored near each other in hospital and community pharmacy shelves, which further increases DMETS' concern regarding the risk of error between Norvasc and .

Post-marketing reports have demonstrated that products with some sound-alike and look-alike similarities that also share an overlapping route of administration, dosage form, strength, and dosing regimen have been associated with an increased risk of error. For example, confusion and errors have been reported between Serzone and Seroquel, and Lamictal and Lamisil. Serzone and Seroquel share the same prefix ("Ser"), and have an overlapping dosage form (tablet), route of administration (oral), strengths (100 mg and 200 mg), and dosing regimen (twice daily). Lamictal and Lamisil share the same prefix ("Lam). Additionally, Lamictal and Lamisil share an overlapping route of administration (oral), dosage form (tablet), dosing regimen (daily), and have similar numerals in their strengths (25 mg vs. 250 mg). Therefore, DMETS believes that the potential or confusion and error should be considered for Norvasc and given the post-marketing experience with Serzone and Seroquel, and Lamictal and Lamisil.

Norvasc [redacted]

Norvasc [redacted]

b. Nuvaring was identified to have sound-alike and look-alike characteristics to [redacted] Nuvaring is a vaginal hormonal contraceptive, which is designed to deliver 120 micrograms of etongestrel and 15 micrograms of ethinyl estradiol per day. Nuvaring is inserted prior to or on day five of the cycle, and left in place for three weeks, then removed for one ring-free week. Both names contain three syllables, and have similar letter combinations [redacted] at the beginning of each name (see page 9). However, the ending of each name is distinguishable when spoken and written [redacted]). Nuvaring and [redacted] also differ in route of administration (vaginal vs. oral), dosage form (vaginal ring vs. tablet [redacted]), strength (11.7 mg, 2.7 mg vs. tablets: 5 mg, 10 mg, 15 mg, and 20 mg, [redacted] and dosing regimen (every three weeks vs. daily). DMETS believes that the above mentioned differences minimize the risk of confusion between Nuvaring and . [redacted]

Nuvaring —

Nuvaring —

c. Avita was found to have sound-alike characteristics to the proposed name, — Avita contains tretinoin, and is indicated for the treatment of acne vulgaris. Both names consist of three syllables, and the ending of each name is phonetically identical — However, the beginning of each name is distinguishable when spoken — Although Avita and — share an overlapping dosing regimen (once daily), they differ in route of administration (topical vs. oral), dosage form (cream and gel vs. tablet and strength (0.025% vs. tablets: 5 mg, 10 mg, 15 mg, 20 mg — . Therefore, DMETS believes that the lack of convincing sound-alike similarities and the differences in route of administration, dosage form, and strength minimize the risk of confusion between Avita and — .

2. Namenda

In reviewing the proprietary name "Namenda", DMETS did not identify any proprietary names with a look-alike and/or sound-alike similarity to Namenda. We conducted prescription studies to simulate the prescription ordering process. Our studies did not confirm confusion between Namenda and currently marketed proprietary names.

III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proposed proprietary name, — due to its potential to sound and look like Norvasc. However, DMETS has no objections to the use of the proprietary name Namenda.

Norvasc has look-alike similarities to the proposed name, — Norvasc contains amlodipine and is indicated for the treatment of hypertension and angina. The recommended dose of Norvasc is 5 mg to 10 mg daily. Both names contain seven letters, and the prefix of each name differs by one letter — The ending of each name is distinguishable when written mainly to due to the upstroke of the letter — However, if the upstroke of the letter is not prominent, the suffixes may look similar. Both drugs also share an overlapping route of administration (oral), dosage form (tablet), strengths (5 mg and 10 mg), and dosing regimen (once daily). Additionally, Norvasc and — will be stored near each other in hospital and community pharmacy shelves, which further increases DMETS' concern regarding the risk of error between Norvasc and —

Post-marketing reports have demonstrated that products with some sound-alike and look-alike similarities that also share an overlapping route of administration, dosage form, strength, and dosing regimen have been associated with an increased risk of error. For example, confusion and errors have been reported between Serzone and Seroquel, and Lamictal and Lamisil. Serzone and Seroquel share the same prefix ("Ser"), and have an overlapping dosage form (tablet), route of administration (oral), strengths (100 mg and 200 mg), and dosing regimen (twice daily). Lamictal and Lamisil share the same prefix ("Lam).

Additionally, Lamictal and Lamisil share an overlapping route of administration (oral), dosage form (tablet), dosing regimen (daily), and have similar numerals in their strengths (25 mg vs. 250 mg). Therefore, DMETS believes that the potential or confusion and error be considered for Norvasc and — given the post-marketing experience with Serzone and Seroquel, and Lamictal and Lamisil.

Norvasc ———

Norvasc —

In addition, DMETS reviewed the blister labels, container labels, and carton and draft package insert labeling for — We have identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

We note on all the labels and labeling an equivalency statement appears with the strength. The statement says "Equivalent to XX mg Memantine Hydrochloride". However, the established name is expressed in terms of the salt. Therefore, the equivalency statement is not necessary. If the salt is removed from the established name then the equivalency statement would be necessary. Revise accordingly.

B. BLISTER LABEL (5 mg, 10 mg, 15 mg, and 20 mg)

1. See General Comment.

2. Revise the dosage form statement to read "Tablet" rather than "Tablets".

3. When comparing the blister tablets side-by-side they look identical. We recommend revising the labels so that each strength is differentiated by contrasting color, boxing, or some other means.

C. BLISTER CARTON LABELING (5 mg, 10 mg, 15 mg, and 20 mg)

1. See General Comment.

2. Please delete the equivalency statement from the back panel.

3. The net quantity statement currently appears on the back panel and is not very distinct. We recommend relocating it to the principal display panel away from the product strength.

D. BLISTER CARTON LABELING (Titration Pak)

1. We note that the sponsor proposes to market the product in a titration pack that includes 5 mg and 10 mg tablets constituting a four week supply of medication. DMETS does not recommend packaging — 5 mg and — 10 mg together, as this increases the potential for medication errors. Although the sponsor indicates that the recommended target dose for — is 20 mg per day, in clinical trials, the effective dose ranged from 10 mg to 20 mg per day. If a patient experiences optimal pharmacological effect with the 10 mg dose, and is given the

titration pack, this would increase the risk of errors such as patients taking the wrong dose. Additionally, the minimum recommended interval between dose increases is one week. If patients require a longer interval this titration pak will not meet their needs.

2. Revise AM and PM to read "Morning" and "Evening". This wording will prevent the medication from being taken at 11:30 am and 12:30 pm.

3. The principal display panel should prominently include the following:

   This titration pack contains:
   4 week supply of Memantine Hydrochloride tablets
   5 mg and 10 mg
   Week 1 – seven 5 mg tablets
   Week 2 – fourteen 5 mg tablets
   Week 3 – seven 5 mg tablets and seven 10 mg tablets
   Week 4 – fourteen 10 mg tablets.

E. CONTAINER LABEL (5 mg, 10 mg, 15 mg, and 20 mg)

1. See General Comment.

2. Please include the dosage form with the established name rather than in conjunction with the product strength. For example:

   Namenda
   (Memantine Hydrochloride Tablets)
   5 mg

3. Ensure that the net quantity appears away from the product strength.

4. Please include a "Usual Dosage" statement on the label per 21 CFR 201.55.

5. Ensure the 60 count unit-of-use bottles has a child-resistant closure (CRC) cap.

F. CONTAINER LABEL (2 mg/mL and 4 mg/mL)

1. See General Comment.

2. [redacted]

3. Ensure that the 120 mL size bottles have a child resistant cap.

G. PACKAGE INSERT LABELING

No comment.

IV. RECOMMENDATIONS

1. DMETS does not recommend the use of the proprietary name [redacted] However, DMETS has no objection to the use of the proprietary name Namenda. DMETS considers this a final review. If the approval of the application is delayed beyond 90 days from the signature date of this review, the name and its associated labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

2. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review.

3. DDMAC finds the names [redacted] and "Namenda" acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

/S/

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/S/

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tia Harper-Velazquez
8/22/03 11:13:02 AM
PHARMACIST

Alina Mahmud
8/22/03 11:14:47 AM
PHARMACIST

Carol Holquist
8/22/03 12:05:40 PM
PHARMACIST

Jerry Phillips
8/25/03 09:26:25 AM
DIRECTOR

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-487	Efficacy Supplement Type SE-	Supplement Number	
Drug: Namenda (Memantine) Tablets		Applicant: Forest	
RPM: Griffis		HFD-120	Phone # 301-594-5526
Application Type: (x) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	Alzheimer's Disease
• Other (e.g., orphan, OTC)	none
❖ User Fee Goal Dates	October 19, 2003
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	( ) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
❖ Actions	
• Proposed action	(x) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	none
• Status of advertising (approvals only)	(x) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (x) Press Release (x) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X (labeling has been negotiated with sponsor)
• Most recent applicant-proposed labeling	N/A-see above
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	See tab C
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	Waiting for FPL of carton & container to be submitted
• Reviews	CMC/DMETS review in tab Q
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes- see approval letter
• Documentation of discussions and/or agreements relating to post-marketing commitments	Fax from sponsor accepting commitments to be sent ASAP
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	See tab R
❖ Memoranda and Telecons	See tab R
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	January 25, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	October 2, 2003
• Other	none
❖ Advisory Committee Meeting	
• Date of Meeting	September 24, 2003
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	DD memo 10/14/03
❖ Clinical review(s) *(indicate date for each review)*	10/2/03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety review(s) *(indicate date or location if incorporated in another review)*	8/20/03
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	See tab F
❖ Statistical review(s) *(indicate date for each review)*	9/29/03
❖ Biopharmaceutical review(s) *(indicate date for each review)*	10/2/03
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	9/30/03
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	See tab H
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	8/20/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: **(x)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	10/9/03
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	8/25/03
❖ CAC/ECAC report	7/31/03

39 pages redacted from this section of the approval package consisted of draft labeling