

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-487

Administrative Documents

SECTION 14: PATENT CERTIFICATION

Patent Certification

Pursuant to 21 CFR 314.53
For NDA # 21,487

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

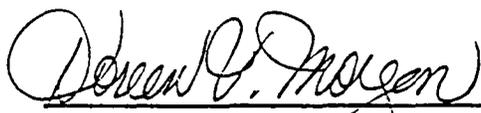
- Trade Name: N/A
- Active Ingredient(s): memantine HCl
- Strength(s): 5, 10, 15, and 20 mg
- Dosage Form: Tablet
- Approval Date: N/A

US Patent Number: 5,061,703
Expiration Date: April 11, 2010
Type of Patent: Method of use

US Patent Number: 5,614,560
Expiration Date: April 11, 2015
Type of Patent: Method of use

Name of Patent Owner: Mertz and Co.

The undersigned declares that the above stated United States Patent covers the method of use for memantine HCl. This product is the subject of the application for which approval is being sought.



Doreen V. Morgan, PharmD, MS
Director, Regulatory Affairs
Forest Laboratories

EXCLUSIVITY SUMMARY for NDA # 21-487 SUPPL #
Trade Name Namenda Generic Name memantine hydrochloride

Applicant Name Forest HFD- 120
Approval Date 10-16-03

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type (SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /x/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

None stated

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /x/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /x/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /x/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /__x_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/
Investigation #2 YES /___/ NO /___/
Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #
Investigation #__, Study #
Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!

Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!
!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!
!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Melina Griffis, R.ph.
Signature of Preparer
Title: Project Manager

Date

Russell Katz, M.D.
Signature of Office or Division Director

Date

CC:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

**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

10/21/03 08:44:32 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-487 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: Decemeber 19, 2003 Action Date: October 19, 2003

HFD-120 Trade and generic names/dosage form: Namenda (memantine hcl) Tablets

Applicant: Forest Lab Therapeutic Class: Alzheimer's Disease

Indication(s) previously approved: none

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of moderate to severe dementia of the Alzheimer's Type

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval _____
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

) FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960

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

/s/

Melina Griffis
10/20/03 09:38:04 AM



FOREST LABORATORIES, INC.
909 Third Avenue
New York, NY 10022-4731

PHONE: 212-421-7850
FAX: 212-750-9152

DEBARMENT CERTIFICATION

Forest Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application (NDA 21,487) for memantine HCl.

A handwritten signature in black ink, appearing to read 'L. Olanoff', is written over a horizontal line.

Lawrence S. Olanoff, MD, PhD
Executive Vice-President, Scientific Affairs
Forest Laboratories, Inc.

A handwritten date '6/14/02' is written in black ink over a horizontal line.

Date

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

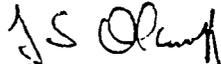
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Lawrence S. Olanoff, MD, PhD	TITLE Executive Vice President, Scientific Affairs
FIRM/ORGANIZATION Forest Laboratories, Inc.	
SIGNATURE 	DATE 7/19/02

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857



Forest Laboratories, Inc.
909 Third Avenue
New York, New York 10022

MEMANTINE NDA #21-487

SECTION 19.0

FINANCIAL DISCLOSURE

FINAL

July 17, 2002

Attachment 1 to FORM FDA 3454:

Clinical Investigators with no disclosable financial arrangements,
for studies (grouped by study) sponsored by the applicant:

Site No.	Principal Investigator	Sub-Investigators
Study MRZ-90001-9403		
01	Dr. Rudite Sarkane Pansionat Gailezers Hipokrata 6 Riga, Latvia LV-1079	N/A
02	Dr. Valda Sevele Pansionat Mezciems Malienas iela 3-7 Riga, Latvia LV-1079	N/A
02	Dr. Ainars Judeikis Pansionat Mezciems Malienas iela 3-7 Riga, Latvia LV-1079	N/A
03	Dr. Vaira Mezule Pansionat No. 1 Telts iela 1 Riga, Latvia-1035	N/A
04	Dr. Erna Haikevica Psychiatric Hospital of the City of Riga Tvaika iela 2 Riga, LV-1005	N/A
04	Dr. Valerijs Grigorjevs Psychiatric Hospital of the City of Riga Tvaika iela 2 Riga, LV-1005	N/A
04	Dr. med. Vladimirs Kuznetsovs Psychiatric Hospital of the City of Riga Tvaika iela 2 Riga, LV-1005	N/A
05	Dr. Skaidrite Parupe Pansionat "Jelgava" Kalnciema ceis 109 Jelgava, LV 3000	N/A

July 17, 2002

Site No.	Principal Investigator	Sub-Investigators
06	Dr. Stefanija Albova Pansjona: "Ropazi" Ropazu pagasts Rigas raj. LV-2135	N/A
07	Dr. Nagezda Starinska Pansjonat of the City of Daugavpils 18 novembra iela 345a Daugavpils. LV-5400	N/A
MRZ 90001-9605		
01	Jeffrey T. Apter, MD <u>Site #1</u> Princeton Biomedical Research, PA 256 Burr Drive, Suite #6 Princeton, NJ 08540 <u>Site #2</u> Princeton Biomedical Research, PA Mule Road Professional Building 9 Mule Road, Suite #E-8 Toms River, NJ 08755	
03	Barry Baumel, MD Baumel-Eisner Neuromedical Institute 7301 North University Drive Suite #205 Ft. Lauderdale, FL 33321	
04	Charles B. Bernick, MD University of Nevada School of Medicine Patient Care Center 1707 West Charleston, Suite #230 Las Vegas, Nevada 89102	
06	John S. Cerman, MD Cerman Research 4015 South Cobb Drive, Suite #245 Smyrna, Georgia 30080	

July 17, 2002

Site No.	Principal Investigator	Sub-Investigators
07	Neil Berwisch, MD Southern New Jersey Medical Institute 9 East Laurel Road Stratford, NJ 08084	
09	Jody Corey-Bloom, MD, PhD Department of Neurosciences (MC9127) UCSD 9500 Gilman Drive La Jolla, CA 92093-9127	
10	Howard Cummins, PhD Institute for Advanced Clinical Research 7900 High School Road Elkins Park, PA 19027-2667	
11	Charles DeCarli, MD University of Kansas Medical Center Department of Neurology 3901 Rainbow Boulevard Kansas City, KS 66160-7314	
12	Rachelie Doody, MD Baylor College of Medicine Department of Neurology 6550 Fannin, Suite #1801 Houston, TX 77030	
13	Ranjan Duara, MD Wien Center for Alzheimer's Disease and Memory Disorders Mount Sinai Medical Center 4300 Alton Road/MRI Building Miami Beach, FL 33140	

July 17, 2002

Site No.	Principal Investigator	Sub-Investigators
14	Eugene DuBoff, MD Denver Center for Medical Research 4704 Harlan Street, Suite #500 Denver, CO 80212	
15	Larry Eisner, MD Baumel-Eisner Neuromedical Institute 7301 North University Drive Suite #300 Fort Lauderdale, FL 33321	
16	Martin R. Farlow, MD Indiana University Center for Alzheimer's Disease Indiana University Hospital 550 University Boulevard Suite #3124 Indianapolis, IN 46202	

July 17, 2002

Site No.	Principal Investigator	Sub-Investigators
17	Steven H. Ferris, PhD New York University Medical Center Aging and Dementia Research Center 550 First Avenue, Room THN314 New York, NY 10016	
18	Stephen Flitman, MD Neurology Group, LTD 500 West Thomas Road, Suite #700 Phoenix, AZ 85013	
20	Noreen Bumby, DO Southwest Institute for Clinical Research 71511 Highway 111, Suite #J Ranch Mirage, CA 92270	
21	Alan Jacobson, PhD Neurological Consultants 1150 North 35 th Avenue, Suite #345 Hollywood, FL 33021	
22	Claire L. Jurkowski, MD Hampton Hospital Behavioral Health Center 650 Rancocas Road Westampton, NJ 08060	
23	Ari Kiev, MD Life Span Developmental Systems 7 Fox Street, Suite #103 Poughkeepsie, NY 12601	

July 17, 2002

Site No.	Principal Investigator	Sub-Investigators
24	Louis C. Kirby, II, MD <u>Site #1</u> Pivotal Research Centers 13260 N. 94 th Drive, Building #200 Peoria, AZ 85381 <u>Site #2</u> Pivotal Research Centers 1525 N. Granite Reef Road, Suite #9 Scottsdale, AZ 85257-3998	
25	David Margolin, MD 6935 N. Fresno Street Suite #102 Fresno, CA 93710	
26	Charles Merideth, MD Affiliated Research Institute 8880 Rio San Diego Drive Suite #1090 San Diego, CA 92108	

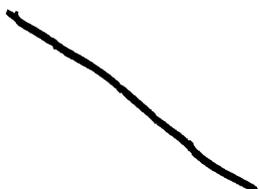
July 17, 2002

Site No.	Principal Investigator	Sub-Investigators
27	Jacob E. Mintzer, MD Alzheimer's Research & Clinical Program 5900 Core Street, Suite #203 Charleston, SC 29406-6076	
28	Eric Pfeiffer, MD USF Suncoast Gerontology Center 10770 N. 46 th Street, Suite A-1200 Tampa, FL 33617	
30	Carl H. Sadowsky, MD Premiere Research Institute Palm Beach Neurological Group South 5205 Greenwood Avenue Suite #200 West Palm Beach, CA 33407	
31	Frederick Schmitt, PhD Sanders Brown Research Center for Aging 101 Sanders-Brown Building 800 South Limestone Lexington, KY 40536-0230	
32	Neil Edwards, MD University of Tennessee Semmes-Murphy Clinic 930 Madison Avenue Suite 700 Memphis, TN 38103	

July 17, 2002

Site No.	Principal Investigator	Sub-Investigators
33	Paul Solomon, PhD The Memory Clinic 100 Hospital Drive Bennington, VT 05201	
34	Steven Targum, MD <u>Site #1</u> Clinical Studies, Philadelphia 400 Market Street, Suite #425 Philadelphia, PA 19106 <u>Site #2</u> Crozer-Chester Medical Center One Medical Center Boulevard Upland, PA 19013 <u>Site #3</u> Clinical Studies, New Jersey 100 Brick Road, Suite #315 Marlton, NJ 08053	
35	Harvey Tilker, PhD <u>Site #1</u> Four Rivers Clinical Research 81 Lakeview Drive Paducah, KY 42001 <u>Site #2</u> Purchase Neurology, Inc. 225 Medical Center Drive Paducah, KY 42001 <u>Site #3</u> John Colby, M.D. 1574 Jefferson Street Paducah, KY 42001	
36	Mahmood Usman, MD Alzheimer's Center of Pittsburgh 5168 Campbells Run Road Pittsburgh, PA 15205	

July 17, 2002

Site No.	Principal Investigator	Sub-Investigators
38	Ralph Richter, MD Clinical Pharmaceutical Trials, Inc. St. John's Doctors Building 1705 E. 19 th Street, Suite #406 Tulsa, OK 74104	

APPEARS THIS WAY
ON ORIGINAL

July 17, 2002

Attachment 2 to FORM FDA 3454:

Clinical Investigators for whom financial disclosure could not be obtained, listed by study, site number, and principle investigator. Forest acted with due diligence to obtain financial information from the following investigators (all of whom were sub-investigators) but was unsuccessful after repeated attempts:

Site No.	Principal Investigator Name & Address	Sub-Investigators	Reason Financial Disclosure Could Not Be Obtained
Study MRZ-90001-9605			
01	Jeffrey T. Apter, MD <u>Site #1</u> Princeton Biomedical Research, PA 256 Bunn Drive, Suite #6 Princeton, NJ 08540 <u>Site #2</u> Princeton Biomedical Research, PA Mule Road Professional Building 9 Muie Road, Suite #E-8 Toms River, NJ 08755		No longer at site.
03	Barry Baumel, MD Baumel-Eisner Neuromedical Institute 7301 North University Drive Suite #205 Ft. Lauderdale, FL 33321		No longer at site.
04	Charles B. Bernick, MD University of Nevada School of Medicine Patient Care Center 1707 West Charleston, Suite #230 Las Vegas, Nevada 89102		No longer at site.
06	John S. Carman, MD Carman Research 4015 South Cobb Drive, Suite #245 Smyrna, Georgia 30080		No longer at site.

July 17, 2002

Site No.	Principal Investigator Name & Address	Sub-Investigators	Reason Financial Disclosure Could Not Be Obtained
07	Neil Berwish, MD Southern New Jersey Medical Institute 9 East Laurel Road Stratford, NJ 08084		No longer at site.
12	Rachelle Doody, MD Baylor College of Medicine Department of Neurology 6550 Fannin, Suite #1801 Houston, TX 77030		No longer at site.
13	Ranjan Duara, MD Wien Center for Alzheimer's Disease and Memory Disorders Mount Sinai Medical Center 4300 Alton Road/MRJ Building Miami Beach, FL 33140		No longer at site.
14	Eugene DuBoff, MD Denver Center for Medical Research 4704 Harlan Street, Suite #500 Denver, CO 80212		No longer at site.
15	Larry Eisner, MD Baumel-Eisner Neuromedical Institute 7301 North University Drive Suite #300 Fort Lauderdale, FL 33321		No longer at site.
16	Martin R. Farlow, MD Indiana University Center for Alzheimer's Disease Indiana University Hospital 550 University Boulevard Suite #3124 Indianapolis, IN 46202		No longer at site.
17	Steven H. Ferris, PhD New York University Medical Center Aging and Dementia Research Center 550 First Avenue, Room THN314 New York, NY 10016		No longer at site.
18	Stephen Filitman, MD Neurology Group, LTD 500 West Thomas Road, Suite #700 Phoenix, AZ 85013		No longer at site.

July 17, 2002

Site No.	Principal Investigator Name & Address	Sub-Investigators	Reason Financial Disclosure Could Not Be Obtained
20	Noreen Bumby, DO Southwest Institute for Clinical Research 71511 Highway 111, Suite #J Ranch Mirage, CA 92270		Did not participate in study per note to file dated 8/3/00. Did not participate in study per note to file dated 6/24/99 (all others).
21	Alan Jacobson, PhD Neurological Consultants 1150 North 35 th Avenue, Suite #345 Hollywood, FL 33021		On 1572 in error, see memo dated 4/14/00 No longer at site (all others).
22	Claire L. Jurkowski, MD Hampton Hospital Behavioral Health Center 650 Rancocas Road Westampton, NJ 08060		No longer at site.
24	Louis C. Kirby, II, MD <u>Site #1</u> Pivotal Research Centers 13260 N. 94 th Drive, Building #200 Peoria, AZ 85381 <u>Site #2</u> Pivotal Research Centers 1525 N. Granite Reef Road, Suite #9 Scottsdale, AZ 85257-3998		No longer at site.
25	David Margolin, MD 6335 N. Fresno Street Suite #102 Fresno, CA 93710		No longer at site.
26	Charles Merideth, MD Affiliated Research Institute 8880 Rio San Diego Drive Suite #1090 San Diego, CA 92108		No longer at site.
27	Jacob E. Mintzer, MD Alzheimer's Research & Clinical Program 5900 Core Street, Suite #203 Charleston, SC 29406-6076		No longer at site.
30	Carl H. Sadowsky, MD Premiere Research Institute Palm Beach Neurological Group South 5205 Greenwood Avenue Suite #200 West Palm Beach, CA 33407		No longer at site.

July 17, 2002

Site No.	Principal Investigator Name & Address	Sub-Investigators	Reason Financial Disclosure Could Not Be Obtained
31	Frederick Schmitt, PhD Sanders Brown Research Center for Aging 101 Sanders-Brown Building 800 South Limestone Lexington, KY 40536-0230		No longer at site.
32	Neil Edwards, MD University of Tennessee Semmes-Murphy Clinic 930 Madison Avenue Suite 700 Memphis, TN 38103		No longer at site.
33	Paul Solomon, Ph.D. The Memory Clinic 100 Hospital Drive Bennington, VT 05201		No longer at site.
34	Steven Targum, M.D. <u>Site #1</u> Clinical Studies, Philadelphia 400 Market Street, Suite #425 Philadelphia, PA 19106 <u>Site #2</u> Crozer-Chester Medical Center One Medical Center Boulevard Upland, PA 19013 <u>Site #3</u> Clinical Studies, New Jersey 100 Brick Road, Suite #315 Marlton, NJ 08053		No longer at site.

July 17, 2002

Site No.	Principal Investigator Name & Address	Sub-Investigators	Reason Financial Disclosure Could Not Be Obtained
35	Harvey Tilker, Ph.D. <u>Site #1</u> Four Rivers Clinical Research 81 Lakeview Drive Paducah, KY 42001 <u>Site #2</u> Purchase Neurology, Inc. 225 Medical Center Drive Paducah, KY 42001 <u>Site #3</u> John Colby, M.D. 1574 Jefferson Street Paducah, KY 42001 <u>Site #4</u> Van M. Woeltz, M.D. 2601 Kentucky Avenue Paducah, KY 42003		Has retired, see note to file dated 5/3/99.
36	Mahmood Usman, MD Alzheimer's Center of Pittsburgh 5168 Campbells Run Road Pittsburgh, PA 15205		No longer at site.
38	Ralph Richter, M.D. Clinical Pharmaceutical Trials, Inc. St. John's Doctors Building 1705 E. 19 th Street, Suite #406 Tulsa, OK 74104		No longer at site.

July 17, 2002

Redacted 10

pages of trade

secret and/or

confidential

commercial

information



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Jon Heiser, M.D.
1601 Dove Street, Suite 290
Newport Beach, California 92660

Food and Drug Administration
Rockville MD 20857

AUG - 4 2003

Dear Dr. Heiser:

Between May 5 and 7, 2003, Ms. Diane C. Van Leeuwen, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol MEM-MD-02 entitled: "A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Memantine in Patients with Moderate to Severe Dementia of Alzheimer's Type") of the investigational drug memantine, performed for Forest Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Van Leeuwen during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

[Faint, illegible text at the bottom of the page, possibly bleed-through or a stamp]

FEI: 3003694508

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

If Headquarters classification is a different classification, explain why:

cc:

HFA-224

HFD-120 Doc.Rm. NDA 21-487

HFD-120 Review Div.Dir. Katz

HFD-120 MO Mani

HFD-120 PM Griffis

HFD-46 c/r/s GCP File #9545

HFD-46 MO Khin

HFD-46 CSO Friend

HFR-PA252 DIB Tucker

HFR-PA2565 BIMO Koller

HFR-PA200 Field Investigator Van Leeuwen

GCF-1 Seth Ray

r/d: (NK): 7/30-7/31/03

reviewed:KMU: 7/03

f/t:/sg:8/4/03

o:\NK_Letters\Heiser072003.nai.doc

Reviewer Note to Rev. Div. M.O.

- An inspection assignment of Dr. Heiser's site was issued in April 2003 per the Review Division's request (HFD-120). Although this site enrolled only 11 subjects out of 395 subjects in protocol MEM-MD-02, it turns out to be an outlier in regard to the primary efficacy analysis. When data from this site is excluded, the p-values for the primary efficacy analysis from significant ($p=0.028$) becomes clearly not significant.
- At this site, 14 subjects were screened and three were screen failures. 11 subjects were enrolled and randomized. Nine subjects completed the study. Reasons for discontinuation of two subjects included an adverse events (subject CLL/9214) and withdrawal of consent (subject JGC/9211).
- An audit of 50% subjects' source records was conducted while the efficacy measures were checked for all subjects. No FDA-483 was issued. Inspectional observation included the data listing inconsistencies between the tabulation submitted by the sponsor and the CRF. For example,

Subject #	End of study score	Sponsor data listing	CRF
9211	SIB	0	73
	ADCS-ADL	0	34
9214	SIB	0	85
	ADCS-ADL	0	7

This inconsistency did not seem to be generated by the site.

- I have conveyed this finding to the review division to see the extent of above problem in the entire data set, to verify with the sponsor as needed and check any impact on study outcome.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Khin U
8/12/03 10:05:03 AM



Food and Drug Administration
Rockville MD 20857

AUG 11 2003

Mahmood Usman, M.D.
5168 Campbells Run Road
Pittsburgh, Pennsylvania 15205

Dear Dr. Usman:

Between April 16 and May 13, 2003, Ms. Cynthia L. Rakestraw, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations:

Protocol MRZ 90001-9605 entitled: "Efficacy and Long-Term Tolerability of Memantine in Patients with Moderately Severe to Severe Alzheimer's Disease;" and

Protocol MEM-MD-02 entitled: "A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Memantine in Patients with Moderate to Severe Dementia of Alzheimer's Type" of the investigational drug memantine, performed for Forest Laboratories, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Rakestraw presented and discussed with you Form FDA-483, Inspectional Observations. We acknowledge receipt of your letter dated June 13, 2003 and wish to emphasize the following:

1. You did not adhere to the investigational plan (21 CFR 312.60).

Protocol MRZ-90001-9605

- a. Subject #140 was enrolled in the study prior to obtaining a brain imaging report and the screening hematology laboratory results as required by the protocol.
- b. The protocol specified the same caregiver/informant will accompany the subject for assessments throughout the study. Subject #040 had a different caregiver/informant at screening and baseline visits. In addition, the protocol-required CIBIC-plus assessment was not conducted at baseline. Yet, you enrolled this subject into the study.

Protocol MEM-MD-02

- c. The protocol required a completed physical examination at the screening visit and at the end of the week 24 (visit 7) or early termination. You did not perform the visit 7 physical examinations for two subjects (#9201 and 9207).
 - d. The protocol specified that all physical examinations must be performed by a physician. For three subjects (#9205, 9210 and 9218), the visit 7 physical examinations were not performed by a physician.
2. You did not promptly report to the sponsor the adverse events experienced by the following subjects [21 CFR 312.64(b)].

Protocol MRZ-90001-9605

Subject 140: visual hallucination

Protocol MEM-MD-02

Subject 9201: insomnia

Subject 9210: skin cancer, fever, sore throat, confusion, dizziness, balance decline

Subject 9218: hallucinations, lack of energy, backpain, lightheadedness, burning eyes,
blurred vision

3. You did not maintain adequate and accurate records [21 CFR 312.62(b)].

Protocol MRZ-90001-9605

- a. There is no documentation to indicate whether a licensed physician or otherwise qualified person performed the required physical/neurological examinations for two subjects (#140 and 226).
- b. For subject 226, changes were made on the results of two Global Deterioration Scale, visit 3/4 Activity of Daily Living and visit 4 Severe Impairment Battery several months after these assessments were done without providing an explanation for the changes.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

Page 3 – Mahmood Usman, M.D.

We appreciate the cooperation shown Investigator Rakestraw during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

JS

Joseph P. Salewski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 4 – Mahmood Usman, M.D.

FEI: 3003947659

Field Classification: OAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response received
- 4)OAI

If Headquarters classification is a different classification, explain why: Requested the investigator to respond to this letter; no strong evidence in the EIR to warrant an OAI classification.

Deficiencies noted:

- failure to adhere to protocol (05)
- inadequate and inaccurate records (06)
- failure to report ADRS (16)

cc:

HFA-224
HFD-120 Doc.Rm. NDA 21-487
HFD-120 Review Div.Dir. Katz
HFD-120 MO Mani
HFD-120 PM Griffis
HFD-47 c/r/s GCP File #10905
HFD-47 MO Khin
HFD-47 CSO Friend
HFR-CE150 DIB Baker
HFR-CE1515 BIMO Tamariello
HFR-CE1515 Field Investigator Rakestraw
GCF-1 Seth Ray

r/d: NK: 6/6-6/9/03
reviewed: AEH:6/10/03; JPS: 6/16/03
revised: NK: 6/16/03; 7/23/03
f/t:ml: 6/11/03
O:\NK_Letters\Usman.vair.doc

Reviewer Note to Rev. Div. M.O.

Protocol MRZ 90001-9605

- At this site, 11 subjects were enrolled. Eight subjects completed the study. Three subjects discontinued from the study. An audit of 5 subjects' records was conducted.
- Inspectional findings:
 - 1) Protocol violations: Subject #140 was enrolled to the study prior to obtaining brain imaging report and hematology laboratory test result. Subject #040 had a different caregiver/informant at screening and baseline visits. In addition, the protocol-required CIBIC-plus assessment was not conducted at baseline because of unavailability of the caregiver. Yet, this subject was enrolled into the study.
 - 2) AE reporting: Subject #140 experienced visual hallucination(visit 5), which was not reported in the CRF.
 - 3) Inadequate record keeping: Source documents for the physical and neurological examination of two subjects (#140 and 226) in protocol MRZ-90001-9605 lacked the signature of the investigator who examined the subjects. There is no documentation to indicate whether a licensed physician or otherwise qualified person performed the required physical/neurological examinations.
For subject #226, changes were made on the results of two Global Deterioration Scale, visit 3/4 Activity of Daily Living and visit 4 Severe Impairment Battery several months after these assessments were done.
- The Review Division should consider excluding data collected from subject 040 with no baseline CIBIC plus data and subject 226 as changes were made several months after ratings were done.
- Otherwise, data appear acceptable.

Protocol MEM-MD-02

- At this site, 16 subjects were enrolled and 15 subjects completed the study. One subject discontinued from the study. An audit of 6 subjects' records was conducted.
- Inspectional findings:
 - 1) Protocol violation: visit 7 physical examinations for two subjects (#9201 and 9207) were not conducted.
 - 2) AE reporting: several AE experienced by three subjects (#9201, 9210 and 9218) during the study, were not reported in the CRF.
- The Review Division should include the non-reported AEs of three subjects in safety database.
- Overall, data appear acceptable.

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

/s/

Joseph Salewski
8/19/03 09:05:29 AM



Dr. Valda Sevele
Pansionat Mezciems
Malienas iela 3-7
Riga, Latvia LV-1079

Food and Drug Administration
Rockville, MD 20857
AUG 13 2003

Dear Dr. Sevele:

Between June 30 and July 3, 2003, Ms. Alicia Mozzachio, Ms. Melissa Garcia and Dr. Ni Khin, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol MRZ 90001-9403 entitled "Efficacy and Tolerability of Akatinal Memantine in Care-Dependent Patients with Moderate to Severe Primary Dementia") of the investigational drug memantine, performed for Forest Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

We understand you did not perform this study under a U.S. Investigational New Drug Application (IND). For your future reference, however, we are providing comments so that you will be aware of FDA's requirements for clinical studies conducted under a U.S. IND.

We provide these comments based on our review of the establishment inspection report, the documents submitted with that report and the Form FDA 483, Inspectional Observations. The provisions of the U.S. Code of Federal Regulations (CFR) that would have been violated had the study been conducted under an IND are provided below for future reference. We acknowledge receipt of your letter dated July 17, 2003 and wish to emphasize the following:

1. You did not adhere to the investigational plan (21 CFR 312.60).
 - a. You enrolled two subjects (049 and 197) who had low vitamin B12 levels of 95 and 67 pmol/L (normal 125-700), respectively, during the screening. The protocol required that there be no clinically relevant reductions of B12 blood levels as one of the inclusion criteria.
 - b. You did not perform vital sign measurements (BP and heart rate) on days 7, 28 and 56 of this study as specified in the protocol for all study subjects.
 - c. The screening procedure (CT scan) for subject 129 was initiated before the legal guardian signed the informed consent for the subject.
2. You did not maintain adequate and accurate records [21 CFR 312.62(b)].
 - a. Laboratory records for subjects 037, 042 and 147 were missing.
 - b. Nursing home records for subjects 44, 45, 142, 143 and 196 did not document a full 12-month history or symptoms of dementia.

Page 2 – Valda Sevele, M.D.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown our FDA personnel during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Handwritten signature in black ink, appearing to read 'K. Maung U' with a horizontal line underneath.

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003996198

Field Classification: Refer to Center

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

Deficiencies noted:

- failure to adhere to protocol (05)
- inadequate and inaccurate records (06)

cc:

HFA-224
HFD-120 Doc.Rm. NDA 21-487
HFD-120 Review Div.Dir. Katz
HFD-120 MO Mani
HFD-120 PM Griffis
HFD-46 c/r/s GCP File #10966
HFD-46 MO Khin
HFD-46 CSO Friend
HFR-CE650 DIB Baumgarten
HFR-CE6520 BIMO Yuscius
HFR-CE600 Field Investigator Mozzachio
HFR-CE250 Field Investigator Garcia
HFC-134 Kadar
GCF-1 Seth Ray

r/d:NK:(8/11/03)

reviewed:KMU:(8/11/03)

f/t:sg:(8/11/03)

O:\NK\ Letters\Sevele.vai.doc

Reviewer Note to Rev. Div. M.O.

- At this site, 41 subjects were enrolled in protocol. One subject (042) died during the study, which was reported to the sponsor as required by the protocol.
- An audit of 19 subjects' records was conducted.
- Limitation to this inspection: the source documents including informed consent were written in Latvian. The majority of exhibits provided in the EIR were in Latvian.
- Inspectional findings included:

Protocol violations

- 1) Two subjects (049 and 197) who had low vitamin B12 levels of 95 and 67 pmol/L (normal 125-700), respectively, during the screening. These subjects were given B12

injections and were enrolled in the study. Protocol stated no clinically relevant reductions of B12 blood levels as one of the inclusion criteria.

- 2) No vital sign (BP and heart rate) measurements were done on days 7, 28 and 56 of this study as specified in the protocol for all study subjects.

Inadequate record keeping

- 1) Laboratory records for subjects 037, 042 and 147 were missing.
 - 2) Nursing home records for subjects 44, 45, 142, 143 and 196 did not document a full 12-month history or symptoms of dementia.
- Overall, efficacy data appear acceptable except for above two subjects with vitamin B12 deficiency.
 - I have conveyed the review division to consider excluding data from these two subjects and to note lack of vital sign measures on days 7, 28 and 56 in safety data.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Khin U
8/14/03 03:33:25 PM



Robert Ashworth, Ph.D.
Senior Director of Regulatory Affairs
Forest Research Institute
A Division of Forest Laboratories
Harborside Financial Center, Plaza V
Jersey City, New Jersey 07311

Food and Drug Administration
Rockville MD 20857

SEP 24 2003

Dear Dr. Ashworth:

Between July 8 and 28, 2003, Mr. Peter R. Lenahan, representing the Food and Drug Administration (FDA), conducted an investigation and met with you and your staff to review your firm's monitoring practices and procedures of clinical studies. The inspection focused on protocol MEM-MD-02 entitled: "A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Memantine in Patients with Moderate to Severe Dementia of Alzheimer's Type" of the investigational drug memantine, performed for Forest Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Lenahan presented and discussed with you Form FDA-483, Inspectional Observations. We wish to emphasize the following:

1. You did not provide an adequate written IND safety report [21 CFR 312.56 (c), 312.32 (c)]

Two serious adverse events reported by the clinical investigators in protocol MEM-MD-02 (T01-USA-02563-01 and 00586-01) were not notified by the sponsor to the FDA in a timely manner. The sponsor's notifications were sent more than two months after the events took place. Each notification should have been made as soon as possible, and not later than 15 calendar days after the sponsor's receipt of the information.

We appreciate the cooperation shown Investigator Lenahan during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 2 – Forest Laboratories, Inc.

FEI: 2434835

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

cc:

HFA-224

HFD-120 Doc.Rm. NDA 21-487

HFD-120 Review Div. Dir. Katz

HFD-120 MO Mani

HFD-120 PM Griffis

HFD-46 c/r/s GCP File #10973

HFD-46 NK/BF

HFR-CE350 DIB Amador

HFR-CE3565 BIMO Isbill

HFR-CE350 Field Investigator Lenahan

GCF-1 Seth Ray

r/d:NK: 9/15/03

reviewed:KMU:9/16/03

f/t:ML:9/22/03

O:\NK\NK_Letters\Forest.vai.doc

Reviewer Note to Rev. Div. M.O.

- This routine sponsor monitoring inspection focused on protocol MEM-MD-02.
- Inspection findings include a delay in reporting SAEs experienced by two subjects during the study.
- Otherwise, data appear acceptable.

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

/s/

Khin U
9/25/03 10:36:41 AM



Rudite Sarkane, M.D.
Pansionat Gailezers
Hipokrata 6
Riga, Latvia LV-1079

Food and Drug Administration
Rockville MD 20857

SEP 25 2003

Dear Dr. Sarkane:

Between July 7 and 9, 2003, Ms. Alicia Mozzachio, Ms. Melissa Garcia and Dr. Ni Khin, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol MRZ 90001-9403 entitled "Efficacy and Tolerability of Akatinal Memantine in Care-Dependent Patients with Moderate to Severe Primary Dementia") of the investigational drug memantine, performed for Forest Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

We understand you did not perform this study under a U.S. Investigational New Drug Application (IND). For your future reference, however, we are providing comments so that you will be aware of FDA's requirements for clinical studies conducted under a U.S. IND.

We provide these comments based on our review of the establishment inspection report, the documents submitted with that report and the Form FDA 483, Inspectional Observations. The provisions of the U.S. Code of Federal Regulations (CFR) that would have been violated had the study been conducted under an IND are provided below for future reference. We acknowledge receipt of your letter dated July 17, 2003 and wish to emphasize the following:

1. You did not adhere to the investigational plan (21 CFR 312.60).
 - a. You enrolled subject 135 who had low vitamin B12 level of 77 pmol/L (normal 125-700) at screening. The protocol required that there be no clinically relevant reductions of B12 blood levels as one of the inclusion criteria.
 - b. You did not perform vital sign measurements (BP and heart rate) for all study subjects on days 7, 28 and 56 of this study as specified in the protocol.
 - c. You enrolled two subjects (028 and 190) who had no schooling or education. The protocol required a minimum of elementary school level education for enrollment in the study.
2. You did not maintain adequate and accurate records [21 CFR 312.62(b)].
 - a. Nursing home records for 8 subjects (003, 019, 024, 036, 135, 138, 188 and 192) did not document a full 12-month history or symptoms of dementia.
 - b. Source records for 8 subjects (005, 006, 010, 019, 020, 022, 024 and 031) did not document the education level of these subjects.

Page 2 – Rudite Sarkane, M.D.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown our FDA personnel during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'K. Maung U.', written over a horizontal line.

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 3 – Rudite Sarkane, M.D.

FEI: 3003996195

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

Deficiencies noted:

failure to adhere to protocol (05)

inadequate and inaccurate records (06)

cc:

HFA-224

HFD-120 Doc.Rm. NDA 21-487

HFD-120 Review Div.Dir. Katz

HFD-120 MO Mani

HFD-120 PM Griffis

HFD-46 c/r/s GCP File #10975

HFD-46 MO Khin

HFD-46 CSO Friend

HFR-CE650 DIB Baumgarten

HFR-CE6520 BIMO Yuscus

HFR-CE600 Field Investigator Mozzachio

HFR-CE250 Field Investigator Garcia

HFC-134 Kadar

GCF-1 Seth Ray

r/d:NK:(9/5/03)

reviewed:KMU:(9/8/03)

f/t:sg:(9/11/03)

O:\NK_Letters\Sarkane.vai.doc

Reviewer Note to Rev. Div. M.O.

- At this site, 48 subjects were enrolled in protocol. Subject 015 and 029 died during the study, which was reported to the sponsor as required by the protocol.
- An audit of 22 subjects' records was conducted.
- Limitation to this inspection: the source documents including informed consent were written in Latvian. The majority of exhibits provided in the EIR were in Latvian.
- Inspectional findings included:

Protocol violations

- 1) **Subject 135 who had low vitamin B12 level of 77 pmol/L (normal 125-700), during the screening. The subject was given B12 injections and enrolled in the study. Protocol stated no clinically relevant reductions of B12 blood levels as one of the inclusion criteria.**
- 2) No vital sign (BP and heart rate) measurements were done on days 7, 28 and 56 of this study as specified in the protocol for all study subjects.

Inadequate record keeping

- 1) Nursing home records for subjects 003, 019, 024, 036, 135, 138, 188 and 192 did not document a full 12-month history or symptoms of dementia.
- Subject 190 had elevated liver enzymes (transaminases) more than twice the upper limit of normal values at screening. Yet, the subject was enrolled in the study. This was reported in both CRF and data listing as protocol violation.
 - In addition, I note that secondary dementia (head trauma) was listed as one of the exclusionary criteria in both the original German version and the version of protocol submitted with the U.S. application. However, the translated protocol used at the sites in Latvia did not include trauma. Instead, trauma was translated as tumor. There were two subjects (**011 and 020**) who had history of head trauma and craniotomy, were included in the study at this center.
 - Overall, efficacy data appear acceptable except for above subjects who did not fulfill all eligibility criteria.
 - I have conveyed the review division to consider excluding data from these subjects and to note lack of vital sign measures on days 7, 28 and 56 in safety data.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Khin U
9/25/03 10:37:48 AM



Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022

MEMANTINE
NDA #21-487

LIST OF INVESTIGATORS

Revision 0.1

July 10, 2002

19.0 FINANCIAL DISCLOSURE

19.1 Introduction

The following section includes financial disclosure information as required in 21 CFR 54. The individual investigator financial disclosure information has been collected for the two pivotal efficacy studies, MRZ 90001-9403 and MRZ 90001-9605; see Attachment 1. However, there are several subinvestigators in the MRZ 90001-9605 study for which this information could not be obtained. Attachment 2 of this section lists all clinical investigators who did not provide financial disclosure and summarizes the "due diligence" on behalf of Forest Laboratories and/or its designees in obtaining this information.

None of the clinical investigators who provided financial disclosure information listed any financial arrangements as described in 21 CFR 54.2. Therefore, an FDA Form 3455 will not be provided.

APPEARS THIS WAY
ON ORIGINAL

July 17, 2002

Completed Clinical Studies

Study No.	Investigator	Center Address
CONTROLLED U.S. CLINICAL STUDIES IN DEMENTIA (CCS)		
MRZ 90001-9605		
	(01) Jeffrey T. Apter, M.D.	<p>Site #1 Princeton Biomedical Research, PA 256 Bunn Drive, Suite #6 Princeton, NJ 08540</p> <p>Site #2 Princeton Biomedical Research, PA Mule Road Professional Building 9 Mule Road, Suite #E-8 Toms River, NJ 08755</p>
	(03) Barry Baumel, M.D.	Baumel-Eisner Neuromedical Institute 7301 North University Drive Suite #205 Ft. Lauderdale, FL 33321
	(04) Charles B. Bernick, M.D.	University of Nevada School of Medicine Patient Care Center 1707 West Charleston, Suite #230 Las Vegas, Nevada 89102
	(06) John S. Carman, M.D.	Carman Research 4015 South Cobb Drive, Suite #245 Smyrna, Georgia 30080
	(07) Neil Berwisch, M.D.	Southern New Jersey Medical Institute 9 East Laurel Road Stratford, NJ 08084
	(09) Jody Corey-Bloom, M.D., Ph.D.	Department of Neurosciences (MC9127) UCSD 9500 Gilman Drive La Jolla, CA 92093-9127
	(10) Howard Cummins, Ph.D.	Institute for Advanced Clinical Research 7900 High School Road Elkins Park, PA 19027-2667
	(11) Charles DeCarli, M.D.	University of Kansas Medical Center Department of Neurology 3901 Rainbow Boulevard Kansas City, KS 66160-7314
	(12) Rachelle Doody, M.D.	Baylor College of Medicine Department of Neurology 6550 Fannin, Suite #1801 Houston, TX 77030
	(13) Ranjan Duara, M.D.	Wien Center for Alzheimer's Disease and Memory Disorders Mount Sinai Medical Center 4300 Alton Road/MRI Building Miami Beach, FL 33140