CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-627

MEDICAL REVIEW

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21627 (000; B2)**
Sponsor:	**Forest Laboratories**
Drug:	**Memantine Oral Solution**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Response To Approvable Letter**
Correspondence Date:	**2/15/05**
Date Received / Agency:	**2/17/05**
Date Review Completed	**3/21/05**
Reviewer:	**Ranjit B. Mani, M.D.**

Executive Summary

Summary Of Submission

The current submission is a Complete Response to a Approvable Letter that was issued by the Agency on February 24, 2004. The Approvable Letter, in turn, was in response to the original submission (dated May 1, 2003) under this application.

This application currently seeks the approval of Namenda® (memantine hydrochloride) oral solution (2 mg/mL) for the treatment of moderate to severe dementia of the Alzheimer's type. Namenda® (memantine hydrochloride) tablets (5 mg and 10 mg) are already approved for the same indication.

New information contained in the original submission consisted of relevant data in the areas of Clinical Pharmacology And Biopharmaceutics, and Chemistry, Manufacturing and Controls, as well as proposed new product labeling. There were no new clinical data contained in that application.

The key deficiency in the original submission under this application was that the proposed product labeling did not describe how individual doses of memantine oral solution were to be accurately measured prior to their administration to patients. The data included in the original submission, together with the efficacy and safety data contained in the earlier-approved NDA 21487 for memantine hydrochloride tablets in the treatment of moderate to severe dementia of the Alzheimer's type, appeared otherwise sufficient to support the efficacy and safety of memantine oral solution for the same indication.

In the current submission, the sponsor has provided what appears to be a reliable means for accurately measuring individual doses of memantine oral solution. Detailed instructions for patients and their caregivers as to how to measure and administer individual doses of memantine oral solution have also been provided. Other changes to the proposed product labeling have been proposed, all of which are acceptable.

Recommendation

I recommend that this application be approved.

1. Background

This submission is intended to be a Complete Response to an Approvable letter that was issued by the Agency on 2/24/04 in answer to the original submission (dated 5/1/03) under this application.

The original submission under this application sought approval for the use of Namenda® (memantine hydrochloride) oral solution (2 mg/mL; 4 mg/mL) for the treatment of moderate-to-severe dementia of the Alzheimer's type. Note that in the current submission, the sponsor is seeking approval for the use of the 2 mg/mL concentration of memantine oral solution, only.

An Approvable, rather than Approval, letter was issued for the original submission under this application as the proposed labeling submitted by the sponsor did not provide for a means of accurately measuring doses of memantine oral solution.

NDA 21487 for the use of the immediate-release tablet formulation of memantine hydrochloride (5 mg and 10 mg) for the treatment of moderate-to-severe dementia of the Alzheimer's type, was submitted on 12/19/02, and was approved by the Division for that indication on 10/16/03. Please see the relevant reviews and the approved labeling for memantine (Namenda®) for further details about that application.

2. Contents Of Current Submission

The current submission contains the following

- Cover letter
- Proposed package insert
- Proposed patient instructions
- Carton and container label
- Chemistry, Manufacturing, And Controls information

3. Contents Of Review

This review will address the following items in the same order as below

- History of application
- System for measuring and administering memantine oral solution
- Proposed changes to labeling
- Consultation from Division of Surveillance, Research, and Communication Support
- Chemistry review
- Labeling comments
- Overall comments
- Recommendation

4. History Of This Application

4.1 Contents Of Original Application

The contents of the original application under this NDA (submitted 5/1/03) are summarized below:

The application sought the approval of Memantine Hydrochloride Oral Solution (2 mg/mL and 4 mg/mL) for the treatment of mild to moderate dementia of the Alzheimer's type.

New information contained in that application consisted of relevant data in the areas of Clinical Pharmacology And Biopharmaceutics, and Chemistry, Manufacturing and Controls, as well as proposed changes to the product labeling. There were no new clinical data contained in that application; none were considered necessary by this Division as a condition for approval of the oral solution formulation of memantine hydrochloride (Namenda®)

In that submission, the sponsor had requested a waiver of evidence of *in vivo* bioequivalence between the immediate-release tablet and oral solution formulations of memantine, based on aqueous solubility, dissolution, and in-vitro permeability data. The Office of Clinical Pharmacology and Biopharmaceutics had granted that waiver and considered the submission acceptable to support the approval of the memantine oral solution formulation

The Office of Chemistry after reviewing that application also considered the submission acceptable to support the approval of memantine oral solution formulation. An Expiration Dating Period of ~ months had been recommended for the drug product,

Microbiology review of this submission had concluded that the drug product was of minimal infective risk. Approval of the application was recommended.

The data included in the submission, together with the efficacy and safety data contained in the earlier-approved NDA 21487 for memantine hydrochloride tablets in the treatment of moderate to severe dementia of the Alzheimer's type, appeared sufficient, except for the deficiency outlined below, to support the efficacy and safety of memantine oral solution for the same indication.

The product labeling contained in this application proposed a dosing regime for the oral solution formulation of memantine that was identical to that contained in the approved product labeling for the tablet formulation; more specifically, it was recommended that dosing began with 5 mg once daily, and be titrated at weekly intervals to a maximum of 10 mg twice daily.

The memantine oral solution drug product was to be available in dosage strengths of 2 mg/mL and 4 mg/mL. The proposed labeling stated that [—] (5 mL) of the 2 mg/mL and 4 mg/mL dosage strengths contained 10 mg and 20 mg, respectively, of memantine hydrochloride but provided no additional directions as to how individual 5 mg and 10 mg doses were to be accurately measured.

The Division observed that [—] was a less accurate means, in general, of measuring individual doses than, for example, a syringe and was not a means at all of measuring a 5 mg dose of the memantine oral solution. The Division also noted that oral

solution formulations of other drugs approved for the treatment of Alzheimer's Disease, such as Exelon® and Reminyl®, contained special instructions as to how individual doses should be measured (with a syringe)

4.2 Key Text In Approvable Letter

The key text contained in the Approvable Letter of 2/24/04 is below

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to describe in the proposed product labeling how individual doses of memantine oral solution will be accurately measured. Currently, you have proposed ——— for measurement, however, ——— is not an accurate means of measuring individual doses, especially for a 5 mg dose of the memantine oral solution. We recommend that you look at approved labeling of other oral solution formulations of drugs for the treatment of Alzheimer's Disease which contain special instructions as to how individual doses should be measured (with a syringe). It is likely that you will also need to prepare a patient/caregiver instruction sheet to provide guidance in preparing and administering appropriate doses.

In addition, it will be necessary for you to submit draft/final labeling revised as follows:

1. Dosage and Administration-See embedded "note to sponsor" comment in the attached approvable labeling.

2. Container Labeling- The term "oral solution" should be part of the established name, and not appear with the strength.

We are recommending an ——— expiration period for this drug product.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

4.3 Sponsor's Proposal Following Approvable Letter

On 4/5/04, the sponsor submitted a proposal, in response to the Approvable Letter, for addressing the key deficiency in this application.

5. System For Measuring And Administering Memantine Oral Solution

As noted earlier, the sponsor has proposed that memantine oral solution be available in a single strength of 2 mg/mL. The formulation is to be dispensed in 360 mL bottles.

The system for measuring and dispensing memantine oral solution consists of an adaptable cap, bottle well tubing, bottle well valve, and valve retainer [redacted] dosing syringe. The syringe itself is comprised of a barrel, plunger, silicone ring-plunger piston, and lubricant.

The system above allows the bottle well tubing to be retained in the bottle.

Details of how this system is proposed to be used are in Section 6.5

6. Proposed Changes To Labeling

The sponsor proposes to use combined labeling for the tablet and oral solution formulations. Changes have been made to selected sections of the labeling only. The base document to which the changes outlined below have been made is the current approved labeling for memantine tablets.

6.1 General Changes

The ™ suffix has been removed from all instances where the word "Namenda" is in the labeling

6.2 DESCRIPTION

The currently proposed text of this section is reproduced below in its entirety. The text highlighted in red text is new

Namenda® (memantine hydrochloride) is an orally active NMDA receptor antagonist. The chemical name for memantine hydrochloride is 1-amino-3,5-dimethyladamantane hydrochloride with the following structural formula:

5 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 1 of 2

emphasize a statement. Bold or enlarge the font. All upper case letters are difficult to read."

8. Chemistry Review

The Chemistry review of this submission was completed by Dr Janusz Rzeszotarski on March 2, 2005.

His conclusions may be summarized as follows

- The instructions as to how to use the dosing device that have been supplied by the sponsor, and included in the Patient Information Sheet, are acceptable
- No Chemistry, Manufacturing, and Controls impact of the submission was noted
- There are no objections to the proposed changes to labeling from the Chemistry, Manufacturing, and Controls perspective
- He has recommended approval of this application.

9. Reviewer's Comments About Labeling

- The changes to the Patient Instruction Sheet recommended by the Division of Surveillance, Research, and Communication Support have been communicated to the sponsor who agreed to incorporate them. Those changes were included in updated "marked-up" proposed labeling submitted by the sponsor on March 17, 2005; no additional changes beyond those contained in the labeling originally included in this submission have been included in the version of proposed labeling submitted on March 17, 2005 (note that the "base" document for this version of labeling consists of the current approved labeling for Namenda®)
- Dr Janusz Rzeszotarski, Chemistry Reviewer, has no objection to the labeling changes proposed by the sponsor.
- The most recent version of the proposed changes to labeling as contained in the submission of March 17, 2005, are acceptable to this reviewer

10. Overall Comments

- The current submission is a Complete Response to an Approvable letter that was issued by the Agency on 2/24/04 in answer to the original

submission (dated 5/1/03) under this application. The original submission under this application sought the approval of memantine oral solution for the treatment of moderate to severe dementia of the Alzheimer's type.

- The key deficiency in the original submission under NDA 21627 was that the proposed product labeling did not describe how individual doses of memantine oral solution were to be accurately measured by caregivers and/or patients. The data included in the original submission, together with the efficacy and safety data contained in the earlier-approved NDA 21487 for memantine hydrochloride tablets in the treatment of moderate to severe dementia of the Alzheimer's type, appeared otherwise sufficient to support the efficacy and safety of memantine oral solution for the same indication.

- In the current submission, the sponsor has provided what appears to be a reliable means for measuring and administering doses of memantine oral solution consisting of an adaptable cap, bottle well tubing, bottle well valve, valve retainer and a dosing syringe. Detailed patient instructions have also been provided.

- The Chemistry reviewer of this submission, Dr Janusz Rzeszotarski, has recommended that this application be approved

- The Division of Surveillance, Research, and Communication Support has recommended a very minor change to the text of the Patient Instruction Sheet which the sponsor has made in a further version of proposed labeling submitted on March 17, 2005.

- The proposed changes to labeling submitted by the sponsor, as most recently contained in the version submitted on March 17, 2005, are acceptable to this reviewer. The deficiency in the original submission under this application has been adequately addressed.

11. Recommendations

I recommend that this application be approved

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 3/21/05
cc:
HFD-120

NDA 21627 (000; B2)

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/s/

Ranjit Mani
3/21/05 08:33:40 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21627**
Sponsor:	**Forest Laboratories**
Drug:	**Memantine Oral Solution**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Original New Drug Application**
Correspondence Date:	**5/1/03**
Date Received / Agency:	**5/2/03**
Date Review Completed	**2/10/04**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Table Of Contents

2. Executive Summary

2.1 Recommendations

I recommend an Approvable action for this application.

For an Approval action to be taken, the sponsor should be asked to describe in the proposed product labeling how individual doses of memantine will be accurately measured; their measurement using [redacted] is inaccurate

2.2 Proposed Indication

This application seeks the approval of Memantine Hydrochloride (Namenda™) Oral Solution (2 mg/mL and 4 mg/mL) **for the treatment of moderate to severe dementia of the Alzheimer's type.**

An immediate-release tablet formulation of memantine (Namenda™) is already approved for the treatment of moderate to severe dementia of the Alzheimer's type. That formulation was approved under NDA 21487.

2.3 Summary Of Contents Of Submission

Key contents of the submission that have been reviewed include

- Chemistry, Manufacturing, and Controls data
- Clinical Pharmacology and Biopharmaceutics data
- Proposed Product Labeling

Sections 4, 5, 6, 8, 10, 11, and 12 of this application are cross-referenced to NDA 21487. Sections 8 and 10 are the Clinical and Statistical sections of the application, respectively.

The application contains no new clinical data.

Individual aspects of this submission are addressed further below

2.3.1 Chemistry, Manufacturing, And Controls Data

The Office of Chemistry considers the submission acceptable for supporting the approval of memantine oral solution.

It has been recommended that an Expiration Dating Period of — months be granted for the memantine oral solution drug product, based on the stability data for the drug product contained in the submission.

2.3.2 Clinical Pharmacology And Biopharmaceutics Data

In this submission, the sponsor has requested a waiver of evidence of in-vivo bioequivalence between the immediate-release tablet and oral solution formulations of memantine, based on aqueous solubility, dissolution, and in-vitro permeability data. The Office of Clinical Pharmacology and Biopharmaceutics has granted that waiver and considers the submission acceptable to support the approval of this application

2.3.3 Cross-Referenced Clinical Data

When the data included in the current submission are considered, the efficacy and safety data contained in the earlier-approved NDA 21487 for memantine hydrochloride (Namenda™) tablets in the treatment of moderate to severe dementia of the Alzheimer's type, appear sufficient to support the efficacy and safety of memantine oral solution for the same indication.

2.3.4 Microbiology Review

Microbiology review of this submission has concluded that the drug product is of minimal infective risk. Approval of the application has been recommended.

2.3.5 Proposed Product Labeling

The product labeling contained in this application proposes a dosing regime for the oral solution formulation of memantine that is no different from that contained in the approved product labeling for the tablet formulation of memantine: it is recommended that dosing begins with 5 mg once daily, and is titrated at weekly intervals to a maximum of 10 mg twice daily.

The memantine oral solution drug product is to be available in dosage strengths of 2 mg/mL and 4 mg/mL. The proposed labeling states that [——] (5 mL) of the 2 mg/mL and 4 mg/mL dosage strengths contains 10 mg and 20 mg, respectively, of memantine hydrochloride but provides no additional directions as to how individual 5 mg and 10 mg doses are to be accurately measured. A [——] is a less accurate means of measuring individual doses than, for example, a syringe and is not a means at all of measuring a 5 mg dose of the memantine oral solution.

For this application to be approved, the sponsor should be asked to describe in the proposed product labeling how individual doses of memantine will be accurately measured. Measurements using [——] will not suffice for that purpose.

3. Background

This submission is an original New Drug Application for the use of memantine oral solution (2 mg/mL; 4 mg/mL) for the treatment of moderate-to-severe dementia of the Alzheimer's type.

NDA 21487 for the use of the immediate-release tablet formulation of memantine for the treatment of moderate-to-severe dementia of the Alzheimer's type, was submitted on 12/19/02, and was approved by the Division for that indication on 10/16/03. Please see the relevant reviews and the approved labeling for memantine (Namenda™) for further details.

In the cover letter, the sponsor has requested a waiver of evidence of in-vivo bioequivalence between the immediate-release tablet and oral solution formulations of memantine, based on aqueous solubility, dissolution, and in-vitro permeability data.

4. Contents Of Submission

This application contains relevant Human Pharmacokinetics and Bioavailability, and Chemistry, Manufacturing, and Controls (drug product) data only, in addition to proposed labeling. Other data are cross-referenced to NDA 21487.

There are no new clinical data contained in this submission

5. Contents Of Review

In this review, I will

- Summarize the conclusions of the clinical pharmacology and biopharmaceutics, chemistry, and microbiology reviewers
- Describe the proposed changes to labeling that are pertinent to the new formulation
- Briefly address the Financial Disclosure Certification section of the application

6. Clinical Pharmacology And Biopharmaceutics Review

This review was performed by Veneeta Tandon, PhD, Clinical Pharmacology and Biopharmaceutics Reviewer.

Her conclusions may be summarized as follows

- Memantine has already been designated as a Biopharmaceutics Classification System (BCS) Class I drug based on the following properties of the approved tablet formulation: high aqueous solubility, high *in vitro* permeability, and rapid dissolution

- The sponsor has supplied sufficient evidence to indicate that the excipients used in the oral solution formulation of memantine, including sorbitol, will not influence the rate and extent of absorption of memantine

Recommendations made in her review are as follows

- The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE-I) has granted a waiver for conducting *in vivo* bioequivalence studies comparing the immediate-release tablet and oral solution formulations of memantine. The grant of this waiver is based on the earlier BCS I classification of memantine.

- This submission is acceptable from the OCPB point of view to support the approval of memantine oral solution.

7. Chemistry, Manufacturing, And Controls Review

The reviewer of this submission was Dr Janusz Rzeszotarski. He considers the application acceptable in support of the approval of memantine oral solution, based on the following

- Stability data for the drug substance and product

- Specifications for the drug substance and product (and their justification)

- Acceptable manufacturing facilities

Dr Maryla Guzewska, Chemistry Team Leader, has recommended that an Expiration Dating Period of — months be granted for memantine oral solution, based on the stability data contained in the submission. Earlier, Dr Rzeszotarski, had in his review, recommended that an Expiration Dating Period of — months only be granted, based on stability studies extending through — months only (at controlled room temperature); Dr Guzewska does not concur with that recommendation and believes that the actual stability data at — months at controlled room temperatures, and at 6 months under accelerated conditions, justify an Expiration Dating Period of — months

8. Product Quality Microbiology Review

This review was performed by Bryan S. Riley, PhD, Microbiology Reviewer.

His conclusions may be summarized as follows

- The drug product is a non-sterile preserved solution
- There are no microbiology deficiencies in the submission
- The drug product has appropriate microbial limit specifications and is adequately preserved. Therefore the drug product is of minimal risk in regard to product quality microbiology

He has recommended approval of this application.

9. Proposed Changes To Labeling

Proposed changes to labeling are to the How Supplied section of the label only. I have reproduced both the Dosage And Administration and How Supplied sections of the label in their entirety below. The only changes seen are those pertinent to the new oral solution formulation and are highlighted in red.

DESCRIPTION

1 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__✓__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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10. Financial Disclosure Certification

The financial disclosure certification contained in the current application is identical to that contained in NDA 21487, which this reviewer has previously found acceptable.

11. Comments And Recommendation

- This application seeks the approval of ~~an~~ Memantine Hydrochloride Oral Solution (2 mg/mL and 4 mg/mL) for the treatment of mild to moderate dementia of the Alzheimer's type. A tablet formulation of memantine hydrochloride (Namenda™) has already been approved for the same indication under ~~IND~~ NDA 21487

- New information contained in this application consists of relevant data in the areas of Clinical Pharmacology And Biopharmaceutics, and Chemistry, Manufacturing and Controls, as well as proposed product labeling. There is no new clinical data contained in the current application

- In this submission, the sponsor has requested a waiver of evidence of in-vivo bioequivalence between the immediate-release tablet and oral solution formulations of memantine, based on aqueous solubility, dissolution, and in-vitro permeability data. The Office of Clinical Pharmacology and Biopharmaceutics has granted that waiver and considers the submission acceptable to support the approval of the memantine oral solution formulation

- The Office of Chemistry reviewing this application also considers the submission acceptable to support the approval of memantine oral solution

formulation. An Expiration Dating Period of — months has been recommended for the drug product,

- Microbiology review of this submission has concluded that the drug product is of minimal infective risk. Approval of the application has been recommended.

- Taking into consideration the data included in the current submission, the efficacy and safety data contained in the earlier-approved NDA 21487 for memantine hydrochloride (Namenda™) tablets in the treatment of moderate to severe dementia of the Alzheimer's type, appears sufficient to support the efficacy and safety of memantine oral solution for the same indication.

- The product labeling contained in this application proposes a dosing regime for the oral solution formulation of memantine that is identical to that contained in the approved product labeling for the tablet formulation; more specifically, it is recommended that dosing begins with 5 mg once daily, and is titrated at weekly intervals to a maximum of 10 mg twice daily.

  The memantine oral solution drug product is to be available in dosage strengths of 2 mg/mL and 4 mg/mL. The proposed labeling states that a teaspoonful (5 mL) of the 2 mg/mL and 4 mg/mL dosage strengths contains 10 mg and 20 mg, respectively, of memantine hydrochloride but provides no additional directions as to how individual 5 mg and 10 mg doses are to be accurately measured. [—] is a less accurate means, in general, of measuring individual doses than, for example, a syringe and is not a means at all of measuring a 5 mg dose of the memantine oral solution.

  Oral solution formulations of other drugs approved for the treatment of Alzheimer's Disease, such as Exelon® and Reminyl®, contain special instructions as to how individual doses should be measured (with a syringe)

  For this application to be approved, the sponsor should be asked to describe in the proposed product labeling how individual doses of memantine will be <u>accurately</u> measured. Measurements using [—] will not suffice for that purpose.

- I recommend an Approvable action for this application.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 2/10/04
cc:
HFD-120
NDA 21627

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/s/

Ranjit Mani
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