CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-224

Medical Review(s)

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21224**
Sponsor:	**Janssen**
Drug:	**Galantamine Oral Solution**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Resubmission**
Correspondence Date:	**4/26/01**
Date Received / Agency:	**5/10/01**
Date Review Completed	**5/15/01**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This submission is the sponsor's response to the "Approvable" action issued by the Agency on December 1, 2000.

This application was originally submitted on 1/31/00. Please refer to my review of the original submission dated 10/19/00 for further details.

Reminyl® (galantamine) is a cholinesterase inhibitor which has been developed in this country under Investigational New Drug application (IND) ( )

The tablet form of Reminyl® was approved by this Agency on 2/28/01 for the treatment of mild-to-moderate dementia of the Alzheimer's type, under NDA # 21169.

2. Text Of Approvable Letter

The text of the approvable letter dated 12/1/00 is below:

NDA 21-224

Janssen Research Foundation
Attention: Charles LaPree
Assitant Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Mr. LaPree:

Please refer to your new drug application (NDA) dated January 31, 2000, received February 3, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reminyl® (galantamine hydrobromide) 4 mg/mL Oral Solution.

We also acknowledge receipt of the following submissions:

August 17, 2000
October 16, 2000

We have completed the review of this application, as amended, and it is approvable. However, since this application relies primarily on data submitted to your companion application for the tablet formulation of Reminyl (NDA 21-169), before it may be approved, it will be necessary that the Reminyl Tablet application be approved, either concurrent with/or before this application. Additionally, it will be necessary for you to submit final printed labeling (FPL) for Reminyl Oral Solution.

We also note that the Reminyl Tablet application received an approvable action letter from the Agency on July 29, 2000, and the Agency is currently reviewing the major amendment dated August 31, 2000 submitted to this application.

Package Insert

With regard to your package insert, a combination package insert for both the tablet and oral solution is recommended. We ask that, once agreement has been reached regarding text for the tablet package insert, a combination insert be prepared and submitted in response to this letter. The combined package insert would initially be reviewed under this application and, after approval, could be submitted as a "Changes Being Effected" supplemental application to the tablet NDA.

With regard to the Instructions for Use for the oral solution, agreement on language will be reached during the resubmission review period. However, it should be included at the end of the package insert, in addition to accompanying the drug product. Furthermore, a paragraph in

labeling under the PRECAUTIONS, Information for Patients and Caregivers section should be included stating the following:

> The caregiver should be instructed in the correct procedure for administering Reminyl Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering Reminyl Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

In addition, as requested in the approvable letter for the Reminyl Tablet application, the name galantamine hydrobromide should be established (package insert and carton and container labeling) as the official USAN name.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

> Division of Drug Marketing, Advertising, and Communications, HFD-40
> Food and Drug Administration
> 5600 Fishers Lane
> Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Melina Fanari, R.Ph., Regulatory Management Officer, at (301) 594-5526.

Sincerely,

/S/

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

3. Contents Of Submission

The submission contains the following:

- A combination package insert for the tablet and oral solution formulation with the items exclusive to the oral solution formulation highlighted
- Instructions for use of the oral solution modified in response to comments received by the Division on 8/14/00. These instructions are part of the package insert.

4. Label

The highlighted sections of the label are as follows

- A description of the concentration and contents of the Reminyl® Oral Solution formulation in the DESCRIPTION section

- The following text added to the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections.

  "The caregiver should be instructed in the correct procedure for administering Reminyl Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering Reminyl Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist".

- A description of how Reminyl® oral solution is supplied and stored in the HOW SUPPLIED section

The rest of the label is identical to the already-approved label for the Reminyl® tablet formulation and does not require further review

5. Patient Instruction Sheet

This instruction sheet provides detailed instructions in a series of photographs as to how to open the bottle containing Reminyl® oral solution and use the supplied pipette.

These instructions are acceptable.

6. Comments And Recommendations

- The package insert included in this application is acceptable to this reviewer
- I recommend that the application be approved.

/S/ 6-13-01

Ranjit B. Mani, M.D.
Medical Reviewer

A. Oliva, M.D. /S/ 6-15-01

rbm 5/15/01
cc:
HFD-120
NDA 21224

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21224**
Sponsor:	**Janssen**
Drug:	**Galantamine Oral Solution**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**New Drug Application**
Correspondence Date:	**1/31/00**
Date Received / Agency:	**9/5/00**
Date Review Completed	**10/19/00**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Introduction

This submission consists of a New Drug Application for galantamine oral solution.

Reminyl® (galantamine) is a cholinesterase inhibitor which has been developed in this country under Investigational New Drug application (IND[ ]

NDA # 21169 for the use of galantamine tablets (4 mg, 8 mg and 12 mg) in the treatment of mild to moderate dementia of the Alzheimer's type was submitted on 9/29/99 followed by an Amendment on 2/25/00. The efficacy review of the original NDA and the amendment, were completed by me on 6/13/00. The safety review of the submission was completed by Drs Judith Racoosin, Jerry Boehm and Kevin Prohaska. Please see these reviews for full details.

Based on these and the other reviews of the above application, an "Approvable" letter was issued on 7/29/00. Please refer to that letter for full details. The letter included the following:

- Draft labeling, revised by the Agency, and containing several "Notes to Sponsor" requesting further revisions or clarifications
- Requests for information and additional analyses pertaining to the safety review
- Requests for information in regard to several toxicology studies, and for specific histopathological examinations in Phase 4
- Requests for information pertaining to Chemistry, Manufacturing and Controls
- A request to adopt a specific dissolution methodology for all galantamine tablets.

The sponsor's response to the Agency's approvable letter was dated 8/31/00 and is currently under review by the Division.

2. Contents Of Submission

The submission contains a summary and full study report for GAL-NED-5, a study that was used to establish the relative bioavailability of the tablet and oral solution formulations of galantamine that were intended for US marketing.

This review will be confined largely to the safety data for GAL-NED-5, only briefly summarizing the pharmacokinetic data provided

3. Chemistry

The concentration of the oral solution formulation of galantamine is 4 mg/mL. The inactive ingredients for this solution are [ ] parahydroxybenzoate, propyl parahydroxybenzoate, sodium saccharin, sodium hydroxide and purified water. Please see the review by Dr Janusz Rzeszotarski, Chemistry Reviewer, for full details.

4. Human Pharmacokinetics

The following is a summary of the human pharmacokinetics of galantamine

Following oral administration the drug has an absolute bioavailability of 88.5 % . It is absorbed fairly rapidly by that route with a t_{max} of 0.5 to 2.5 hours, but absorption is delayed by the presence of food. Protein-binding is low at 18 %. Metabolism in humans appears to occur through at least 5 pathways. The main products of Phase I metabolism have been identified as O-desmethyl-galantamine and galantamine-N-oxide, formed through CYP2D6 and CYP3A4, respectively. An active metabolite present in relatively low concentration is N-desmethyl-galantamine (norgalantamine). The terminal half-life ranges from about 7-8 hours. The pharmacokinetics of galantamine appear to be linear up to a dose of 36 mg/day. In moderate hepatic impairment exposure to galantamine (based on AUC) increased by about 33 %. In moderate and severe renal impairment, exposure to galantamine increased by 67 % and 37 %, respectively. Galantamine appeared to have a low potential for inhibiting the major CYP450 pathways. Concurrent use of ketoconazole and paroxetine increased the AUC of galantamine by 30 % and 40 %, respectively. No significant interactions have been seen with warfarin, digoxin, cimetidine, ranitidine and erythromycin.

Please see the combined Clinical Pharmacology and Biopharmaceutics review of NDAs 21169 by Sayed Al-Habet, Ph.D., for full details about the pharmacokinetics of the oral solution formulation of galantamine, including its relative bioavailability in relation to the tablet formulation. **Dr Al-Habet has concluded that the oral solution formulation (4 mg/mL given in a dose of 3 mL) of galantamine is bioequivalent to the 12 mg US market tablet formulation, when both are administered in a dose of 12 mg b.i.d.**

5. Study GAL-NED-5

5.1 Title

Relative Bioavailability Of Galantamine After Repeated Oral Dosing As The Us Market Tablet Formulation Or As An Oral Liquid In Healthy Subjects

5.2 Objective

To compare the relative bioavailability of the US market 12 mg tablet formulation and the oral solution formulation of galantamine when each is given in 12 mg doses.

5.3 Design

Randomized, open-label, 2-way cross-over trial

5.4 Duration

4 weeks (including 2-week period of titration to dose of 12 mg b.i.d)

5.5 Dosage

The following titration and maintenance schedule for galantamine was used for the trial.

4 mg b.i.d for 1 week followed by
8 mg b.i.d for 1 week, further followed by
12 mg b.i.d for 2 weeks

Details regarding what formulation was used at specific times in the study are in the following table

Study Days	Dose	Formulation
1-7	4 mg b.i.d	Tablet (all subjects)
8-14	8 mg b.i.d	Tablet (all subjects)
15-21	12 mg b.i.d*	Tablet or oral solution**
22-28	12 mg b.i.d*	Tablet or oral solution**

*Treatment A: tablet
Treatment B: oral solution
**The 2 formulations were randomly allocated on Days 15 and 21. Those receiving the oral solution from Days 15-21 received the tablet from Days 22-28 and vice versa

Assessments were performed at the end of each 1-week treatment period with galantamine; it was presumed that, based on a galantamine elimination half-life of 9 hours, blood levels would reach a steady-state after 7 days of treatment at 12 mg b.i.d.

5.6 Sample Size

30 subjects

5.7 Main Inclusion Criteria

- Male
- 18-45 years old
- Non-smoking or smoking no more than the following for at least 6 months prior to selection: 10 cigarettes, 2 cigars or 2 pipes
- Body Mass Index: 18-28 kg/m^2
- Healthy on the basis of screening medical history, physical examination, electrocardiogram and safety laboratory tests (hematology, clinical chemistry, urinalysis) carried out < 3 weeks before the first dose (if abnormalities were present they must have been considered clinically insignificant)
- Informed consent

5.8 Main Exclusion Criteria

- Drug or alcohol abuse
- Relevant history of cardiac arrhythmias, bronchospasm, cardiovascular diseases, diabetes mellitus, thyrotoxicosis, parkinsonism, drug allergy or hypersensitivity
- Bradycardia (heart rate < 55 beats per minute)
- Use of concomitant medication other than acetaminophen; all other medications had to be stopped 14 days prior to the start of the study
- Febrile illness less than 72 hours prior to first dose of study medication
- Use of an investigational drug within 30 days prior to the first dose

- Blood donation within 60 days prior to the first dose

5.9 Concomitant Medications

Apart from the above subjects were not allowed to consume grapefruit juice or beverages containing alcohol or quinine while at the study location.

5.10 Schedule

- Pharmacokinetic blood samples were drawn before the morning dose on Days 1, 19, 20, 21, 27 and 28. On Days 21 and 28 they were also drawn at the following times after the morning dose: 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours
- Vital signs and electrocardiograms were checked at screening, at study discharge, and on Days 8 and 15 immediately before and 2 hours after the morning dose
- Safety laboratory tests were checked at screening and prior to study discharge
- Adverse events were checked throughout the study

5.11 Outcome Measures

5.11.1 Pharmacokinetics

Plasma levels of galantamine

5.11.2 Safety

Adverse events, vital signs, electrocardiograms and safety laboratory tests*
*hematology, clinical chemistry and urinalysis

5.12 Analysis Plan

- Descriptive statistics were provided for age, body weight, height and Body Mass Index
- Pharmacokinetic parameters to be calculated included C_{min}, C_{max}, t_{max}, AUC_τ, C_{av} and FI (Fluctuation Index). These were to be further analyzed as follows
  - All subjects participating in the trial were to be used in the analysis
  - For each treatment descriptive statistics were calculated for the plasma concentrations at each sampling time and for the derived pharmacokinetic parameters
  - The C_{min}, C_{max}, AUC_τ, C_{av} and FI were analyzed using ANOVA using a general linear model which included factors of sequence, subject, period and treatment. Tests were conducted at the 0.05 level of significance (2-tailed)
  - Differences in t_{max} between Treatments A and B were statistically evaluated using Koch's procedure at a 0.05 level of significance
  - Geometric mean ratios and associated 90% confidence intervals were calculated for the treatment ratio B/A of the log-transformed C_{min}, C_{max}, and AUC_τ using the mean square error for the ANOVA
  - Bioequivalence between formulations was to be declared if the 90% confidence intervals for the treatment ratio of the log-transformed C_{min}, C_{max}, and AUC_τ were confined in the pre-defined equivalence range of 0.80 to 1.25
  - Descriptive statistics of the pre-dose plasma concentrations of galantamine in the morning were used to document that steady-state concentrations had been achieved
- The safety analysis was performed as follows
  - The type and incidence of all adverse events was tabulated per treatment group
  - Serious adverse events and adverse event dropouts were recorded
  - For clinical laboratory data descriptive statistics and pre- versus post-treatment cross-tabulations were generated for all tests performed
  - Descriptive statistics were provided for electrocardiograms and vital signs

5.13 Results

5.13.1 Disposition

30 subjects received study medication.

3 subjects discontinued the study prior to completion: 2 subjects discontinued the study on Day 15 and one subject on Day 29.

27 subjects were included in the final bioequivalence analysis

5.13.2 Protocol Deviations

These were minor except for a single patient who received metoclopramide 20 mg on Day 28

5.13.3 Demographic And Other Baseline Characteristics

These are summarized in the following table

Variable	Mean	Range
Age	30 years	20 to 43 years
Weight	78 kg	63 to 97 kg
Height	182 cm	168 to 191 cm

5.13.4 Concomitant Medication

A number of subjects used acetaminophen. A single subject used metoclopramide 20 mg on Day 28

5.13.5 Treatment Compliance

All patients took medication as prescribed

5.13.6 Pharmacokinetic Results

These are summarized below

- At steady-state no differences were seen in t_{max} between the 2 galantamine formulations
- Mean and standard deviations for the key parameters are summarized in the following table

Parameter	Treatment A (tablet)	Treatment B (oral solution)
C_{min} (ng/mL)	30.7 ± 10.3	29.8 ± 10.2
C_{max} (ng/mL)	89.4 ± 18.3	87.6 ± 20.5
AUC_τ (ng.hr/mL)	623 ± 147	606 ± 156

- Least squares mean bioequivalence ratios (B/A) are in the following table

Parameter	B/A ratio	90% confidence limits for B/A ratio
C_{min}	97.2%	93.4 to 101.1%
C_{max}	97.5%	90.5 to 104.9%
AUC_τ	97.0%	91.3 to 102.9%

5.13.7 Safety Results

5.13.7.1 Deaths, Serious Adverse Events And Adverse Event Discontinuations

No events in these categories occurred during the study

5.13.7.2 All Adverse Events

These are summarized in the following table which I have adapted from one provided by the sponsor. The table indicates the number of subjects in each group with a specific adverse event

	Number Of Subjects Per Treatment			
Adverse Event	4 mg b.i.d (Tablet)	8 mg b.i.d (Tablet)	Treatment A 12 mg b.i.d (Tablet)	Treatment B 12 mg b.i.d (Oral Solution)
Agitation	1	0	0	0
Asthenia	0	1	0	1
Belching	0	1	0	0
Collapse	0	0	1	0
Common Cold	0	1	1	1
Concentration Impaired	0	0	1	0
Diarrhea	1	0	0	2
Dizziness	0	4	1	2
Dry skin	1	0	0	0
Dyspepsia	0	0	0	1
Fatigue	0	1	1	2
Flatulence	2	0	0	0
Headache	2	5	5	7
Heavy Eyelids	0	0	1	0
Hot Flushes	0	0	1	0
Increased Salivation	1	0	0	0
Increased Sweating	0	1	0	0
Inertia	0	0	1	1
Insomnia	5	3	4	0
Leukocytosis	0	0	0	1
Loose Stools	1	0	0	0
Muscle Cramps	0	1	0	0
Muscle Cramps In Hands	1	1	1	0
Muscular Hypertonia	1	0	0	0
Nausea	1	5	4	6
Inflammation	1	1	1	0
Sore Throat	0	0	1	0
Toothache	1	0	0	0
Vision Abnormal	0	0	0	1
Vomiting	1	2	1	2
Total Number Of Subjects With Adverse Events	13	13	16	13
Total Number Of Subjects	30	29	29	28

As the above table indicates specific adverse events were, in general, infrequent across treatment groups. They were no more frequent in those receiving the oral solution formulation in a dose of 12 mg b.i.d than in those who received the tablet formulation in the same dose

5.13.7.3 Laboratory Data

Clinically significant laboratory abnormalities were seen in 4 patients

- An elevated serum sodium in 1 patient
- An elevated serum sodium and potassium in 1 patient
- An elevated serum potassium in 1 patient
- Neutrophilia in 1 patient

All these abnormalities were not present when the tests were repeated

5.13.7.4 Vital Signs And Electrocardiograms

No clinically significant changes were seen with galantamine (I have read through the individual patient data listings in detail)

5.14 Sponsor's Conclusions

- The oral solution (4 mg/mL) and tablet (12 mg) formulations of galantamine are bioequivalent when both are given in a dose of 12 mg b.i.d., with respect to rate and extent of absorption
- Both the tablet and oral solution formulations were safe and well-tolerated; both preparations were comparable in this regard.

6. Labeling Review

6.1 Sponsor's Draft Label

The sections of the sponsor's draft label that apply exclusively to the oral solution formulation, and not to the tablet formulation, are reproduced below

DESCRIPTION
REMINYL® is also available as a 4 mg/mL oral solution. The inactive ingredients for this oral solution are [ ]parahydroxybenzoate, propyl parahydroxybenzoate, sodium saccharin, sodium hydroxide and purified water

HOW SUPPLIED
REMINYL® (galantamine) 4 mg/mL (NDC 50458-399-10) is a clear colorless solution supplied in 100 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.5 mL, while the maximum calibrated volume is 4 mL.

Storage and Handling
REMINYL® oral solution should be stored at room temperature[ ]DO NOT FREEZE

6.2 Reviewer's Comments

- The above sections of the label will be evaluated by the Chemistry reviewer
- Included in the label is a Patient Information Sheet describing the use of the dispensing pipette to draw galantamine oral solution from the storage bottle. Instructions regarding storage are also provided. The instructions contained in this sheet are sufficiently explicit
- The Clinical Pharmacology and Biopharmaceutics reviewer has recommended the inclusion of the following statement in the Absorption, Distribution, Metabolism and Excretion section of the package insert

  Relative bioavailability from tablets compared with the oral solution is 100%

7. Financial Disclosure Certification

7.1 Sponsor's Financial Disclosure Or Certification Statement

- The sponsor has certified that it has not entered into any financial agreement with the clinical investigators listed in the application whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)
- The sponsor has further certified that no investigator was granted a proprietary interest in the product as defined by 21 CFR 54.2 (c)

- Since none of the clinical trials contained in the application was ongoing on 2/2/99, in accordance with 63FR72181 (12/31/98), no information was collected retroactively from clinical investigators regarding significant equity interest or significant payments of other sorts as defined in 21 CFR 54.2(b) & (f)

7.2 Reviewer's Comment

The sponsor's financial disclosure or certification statement is acceptable

8. Comments And Conclusions

- Based on the results of the GAL-NED-5 study, the oral solution (4 mg/mL) and US market tablet (12 mg) formulations of galantamine do meet Agency standards for bioequivalence when both are given in a dose of 12 mg b.i.d. The Clinical Pharmacology and Biopharmaceutics Reviewer of this submission, Dr Sayed Al-Habet, concurs with this view and states the mean bioavailability of the 12 mg US market tablet of galantamine was 100% relative to the oral solution formulation (4 mg/mL)
- There appear to be no differences in safety and tolerability between the 2 formulations when each is used in a dose of 12 mg b.i.d for 2 weeks, and in the small population of healthy men studied

9. Recommendation

This New Drug Application should be granted the same status as NDA # 21169 for the tablet formulation of galantamine. Currently NDA # 21169 has "Approvable" status.

/S/ 5/11/01

Ranjit B. Mani, M.D.
Medical Reviewer

R. Katz, M.D. /S/

rbm 10/19/00
cc:
HFD-120
NDA 21224
Fanari