CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-169

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-169

FEB 28 2001

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 September 29, 1999, received September 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reminyl® (galantamine hydrobromide) Tablets.

We acknowledge receipt of your submissions dated:

August 3, 2000	October 2, 2000	December 5, 2000	January 23, 2001
August 31, 2000	October 12, 2000	January 17, 2001	January 30, 2001
September 12, 2000	December 1, 2000	January 18, 2001	February 6, 2001

Your submission of August 31, 2000 constituted a complete response to our July 29, 2000 approvable action letter.

This new drug application provides for the use of Reminyl® (galantamine hydrobromide) Tablets for the treatment of mild to moderate dementia of the Alzheimer's type.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format*-NDAs (January 1999).

For administrative purposes, this submission should be designated "FPL for approved NDA 21-169." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated August 31, 2001, to provide the histopathological examinations on cervices of all animals in the rat carcinogenicity study.

Reference is made to your correspondence submitted within this NDA, requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Reminyl® for the treatment of mild to moderate dementia of the Alzheimer's type for the pediatric population.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

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.

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-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

{See appended electronic signature page}

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

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JUL 29 2000

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 September 29, 1999, received September 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reminyl® (galantamine hydrobromide) Tablets.

We acknowledge receipt of your submissions dated:

November 12, 1999	April 13, 2000	June 8, 2000
January 27, 2000	April 20, 2000	June 27, 2000
February 25, 2000	May 25, 2000	

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues:

Labeling

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Reminyl® tablets upon approval. Although sections of this proposal are taken verbatim from the labeling proposed by you in the NDA, other sections have been revised. Please note that we have embedded several "Notes to Sponsor" in the text of the attached draft labeling, requesting further revisions or clarifications.

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

Safety

1. Please explain the discrepancy in the person-time exposure by treatment group in 93-01X and 93-01XX between the study report and the ISS-A (amendment dated February 25, 2000) admsum.xpt dataset.

2. We have determined that in the extension trials of ≤ 12 months in duration, there is a twofold mortality excess in patients originally randomized to galantamine as compared to

those originally randomized to placebo. One possible explanation for this finding is confounding by indication. Please compare the severity of illness of the GAL-GAL patients as compared to the PLA-GAL patients at the time of entry into the first long-term extension by examining concomitant medications, co-morbid conditions, and adverse events experienced during the RCT to investigate this possibility. If confounding by indication is not supported by the data, please put forth an explanation for the difference in mortality described above.

3. Our safety review found that verbatim terms coded to the AE preferred term "injury" included not just injuries, but also planned and unplanned surgical procedures. Given the common occurrence of injury in the study population, please recalculate the risk of discontinuation due to the AE "injury", the frequency of the SAE "injury", and the overall frequency of the AE "injury" across treatment groups and studies after excluding any verbatim terms that do not describe accidental injuries.

4. On review we observed several instances in which the same or similar verbatim terms were coded to several different AE preferred terms describing cardiac abnormalities. These terms included arrhythmia, arrhythmia atrial, arrhythmia ventricular, AV block, bradycardia, bundle branch block, ECG abnormal, ECG abnormal specific, extrasystoles, fibrillation atrial, heart block, QT prolonged, sick sinus syndrome, sinoatrial block, tachycardia, tachycardia supraventricular, and tachycardia ventricular. Please reexamine all AE verbatim terms coded to these preferred terms and reclassify them in a consistent manner to the most appropriate preferred term. Following reclassification, please recalculate new incidences for these events across treatment groups and studies.

5. Please explain how the incidence of falls was calculated given that verbatim terms describing falls were coded to a variety of AE preferred terms including the following: back pain, dizziness, fracture pathologic, joint dislocation, orthostatic hypotension, purpura, and syncope.

6. All verbatim terms containing spasm or cramp should be examined for appropriate assignment to such preferred terms as back pain, cramps legs, leg pain, myalgia, muscle contraction involuntary, and muscle weakness. Following reclassification, please recalculate new incidences for these events across treatment groups and studies.

7. Please review the clinical histories of patients who had glucose measurements less than 60 mg/dl or who had AEs or SAEs of hypoglycemia to try to identify risk factors. Additionally, please look for hypoglycemia outliers using cutoffs of 75 mg/dl, 60 mg/dl, and 45 mg/dl in groups stratified by use of medical therapy for diabetes (e.g. all users vs. non-users).

8. In the RCTs, please examine the frequency of heart rate and rhythm AEs among patients taking both digoxin and galantamine hydrobromide, digoxin alone, galantamine alone, and neither drug. Please also perform mean change from baseline and outlier analyses for heart rate as measured on vital signs and ECG and for PR interval as measured on ECG

for the groups designated above. In a separate analysis, please repeat the above analysis, but examine patients taking beta blockers, verapamil, or diltiazem. Finally, please repeat the original analysis combining the digoxin users with the users of beta blockers, verapamil, or diltiazem.

9. There were several individual patients mentioned in the NDA who suffered adverse events, but for whom pertinent information about the AE was not available in the NDA submission or the amendment to the NDA. Please review your records for the pertinent information on the following patients:

a) In GAL-FRA-1, the study report described one subject with a clinically significant decrease in platelet count at the post-study visit. What were the baseline and end-of-study platelet counts?

b) Patient INT-3/A03057 developed jaundice and was removed from the trial for this reason. Please provide the patient's total bilirubin, AST, ALT, and alkaline phosphatase values at baseline and at the time of discontinuation (and any that were measured in between). What kind of work-up did the patient have for the jaundice and what was the outcome?

c) Patient 95-05X/B0406 was reported to have the AE "hepatic failure", yet it was evaluated as mild and non-serious. What were the patient's LFT values that led to the reporting of this AE?

d) Patient USA-6/A50135 was an 84 year old female who received galantamine hydrobromide during an RCT and continued on galantamine during this extension trial. She developed pancreatitis and was hospitalized. No other details from the hospitalization were available. Please examine your records for information about the patient's pancreatitis including amylase and lipase values, abdominal CT scan findings, and any other pertinent tests. What was the outcome?

e) Patient USA-10/A73226 developed early renal failure during the trial and was discontinued for this reason. Please provide the patient's BUN and creatinine at baseline and at the time of discontinuation (and any other measurements between those times). What was the outcome?

f) Patients USA-10/A73639 and USA-3/A50173 both developed substantial falls in hemoglobin during their respective trials. In each of these patient's narratives, no information was provided concerning the patient's work-up for the cause of the anemia. Please provide any available information to explain the source of these two patients' anemia.

Pharmacology

1. Regarding the mouse lymphoma assay, cell survival in the main study should be presented as % of control. Please address the question of why survival appeared to be greater in Experiment 2 than in Experiment 1 (i.e. there were fewer negative wells in the former), and why, with the exception of Experiment 1 in the presence of S9, survival appeared to be greater in the drug groups than in controls.

2. Regarding the CHO chromosome aberration assay, historical control data should be submitted to indicate 1) the number of studies on which they are based, and 2) the range of mean values across all studies. Only studies using the same solvent as in the galantamine hydrobromide studies should be included unless you can justify including others.

3. We ask that you perform histopathological exams on cervices of all animals in the rat carcinogenicity study in order to help determine if there was a true drug effect on this organ. These can be conducted in Phase 4 but require your written commitment as part of your resubmission.

Chemistry, Manufacturing and Controls

1. We refer you to our information request letter of June 29, 2000 and the DMF [ ] deficiency letter of March 16, 2000 which require your response.

2. We note that, despite our numerous requests, the name galantamine hydrobromide has not been established as an official USAN name. Please attend to that issue.

Biopharmaceutics

1. Please adopt the following dissolution methodology for all strengths of galantamine hydrobromide tablets:

Apparatus II:	USP (Paddles)
Speed:	rpm
Medium:	mL water
Specification:	Not less than % (Q), in minutes

Under 21 CFR 314.50(d)(5)(vi)(*b*), we ask that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those

involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

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/ 7/29/00

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