

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-169

Administrative Documents

PATENT AND EXCLUSIVITY INFORMATION

REMINYL® (galanthamine) Tablet – New Drug Application

Active Ingredient: Galanthamine
Strength: 4 mg, 8 mg and 12 mg
Dosage Form: Tablet
Route of Administration: Oral

Patent and Exclusivity Information:

U.S. Patent Number: 4,663,318
Expiration Date: January 15, 2006
Type of Patent: Method of Use
Name of Patent Owner: Synaptech, Inc.
17 Seacrest Drive
Huntington, N. Y. 11743

The undersigned declares that Patent 4,663,318 covers the formulation, composition, and/or method of use of REMINYL® (galanthamine) Tablet. This product is the subject of this application for which approval is being sought.

Date: September 10, 1999


Mary A. Appollina
Attorney for Applicant
Registered Patent Attorney
Registration No. 34,087

Exclusivity Summary Form

Trade Name: Reminyl

Generic Name: Galantamine

Applicant Name: Janssen

HFD#: HFD-120

Approval Date If Known: 2/28/01

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 question 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 / / NO / /

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

The applicant requested 5 years of marketing exclusivity.

- e) Has pediatric exclusivity been granted for this Active Moiety? NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade? YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 / /

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

2. Combination product – not applicable

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# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. 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."

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 8.

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.

(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 8:

(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /__/_/

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

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 /___/

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

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"):

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 /___/

If no, explain:

Investigation #2 IND # _____ YES /___/ NO /___/

If 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 IND # YES /___/ NO /___/

If no, explain:

Investigation #2 IND # _____ YES /___/ NO /___/

If 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:

S

Signature: _____ **Date:** _____
Melina Fanari, R.Ph., HFD-120

Title: Regulatory Management Officer S

Signature of Office/Division Director

Signature: _____ **Date:** _____
Russell Katz, M.D., Director, HFD-120

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 21169 **Trade Name:** REMINYL(GALANTHAMINE) 4MG/8MG/12MG TABLET
Supplement Number: **Generic Name:** GALANTHAMINE
Supplement Type: **Dosage Form:** TAB
Regulatory Action: PN **Proposed Indication:** Treatment of Alzheimer's Disease

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Does Not Apply
Formulation Status .
Studies Needed .
Study Status .

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,
MELINA MALANDRUCCO

Signature

Date

131
4-19-00

Pediatric Use Waiver

In accordance with 21 CFR 314.55(c)(2), we are hereby applying for a full waiver of the provision to provide pediatric use information for REMINYL® (galantamine) Tablets. The proposed indication for REMINYL® is the "treatment of mild to moderate dementia of the Alzheimer's type". As listed in the December 2, 1998 Federal Register Notice, "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule" [[Page 66648]], Alzheimer's disease is a disease for which a waiver will likely be granted due to the fact that the disease does not have sufficient significance in the pediatric population.

Robin A. Keen

Robin A. Keen
Assistant Director, Regulatory Affairs

29 September 1999

Date

Debarment Certification

In accordance with the Generic Enforcement Act of 1992, we certify that Janssen Research Foundation did not and will not use in any capacity the services of any person or firm debarred under subsections (a) or (b) [section 306 (a) or (b) of the Federal Food, Drug, and Cosmetic Act] in connection with NDA 21-169 for REMINYL® (galantamine) Tablets.

We also hereby certify that flawed Intel Pentium computer chips were not used to perform any analyses included in NDA 21-169.

Janssen Research Foundation verifies that all trials conducted in the United States that are used to support NDA 21-169, were conducted in compliance with the Institutional Review Board regulations in 21 CFR Part 56 and the informed consent regulations in 21 CFR Part 50. Non-US protocols used to support the claims in this application were reviewed by independent Ethics Committees / Review Boards and these trials were performed in accordance with the declaration of Helsinki and its subsequent revisions.



Robin A. Keen
Assistant Director, Regulatory Affairs



Date

Financial disclosure or certification statement

In compliance with 21 CFR 314.50 (k), Janssen Research Foundation is submitting this certification in support of the New Drug Application for REMINYL ® (galantamine) Tablets.

I certify that Janssen Research Foundation has not entered into any financial agreement with the clinical investigators listed in this application 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 further certify that no investigator was granted a proprietary interest in the product as defined in 21 CFR 54.2(c).

Please note that none of the clinical trials contained in this New Drug Application were ongoing as of February 2, 1999. Therefore in accordance with 63 FR72181, December 31, 1998, 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), respectively.

Robin A. Keen

Robin A. Keen
Assistant Director, Regulatory Affairs

29 September 1999

Date

MEMORANDUM

DATE: February 13, 2001

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

TO: File, NDA 21-169

SUBJECT: Recommendation for Action on NDA 21-169, for the use of Reminyl (galantamine hydrobromide) Tablets in patients with Alzheimer's Disease

NDA 21-169, for the use of galantamine hydrobromide tablets, a cholinesterase inhibitor, in patients with Alzheimer's Disease, was submitted by Janssen Research Foundation on 9/29/99. It was the subject of an Approvable letter dated 7/29/00. In that Approvable letter, we asked the sponsor a number of clinical (safety), pharmacology, and CMC questions. In addition, we asked them to adopt specific dissolution specifications.

The sponsor responded with a submission dated 8/31/00. This submission (and subsequent submissions requested by division staff) has been reviewed by Dr. Ranjit Mani, medical officer (review dated 11/29/00), Dr. Judy Racoosin, Safety Team Leader (review dated 1/31/01), and Drs Racoosin and Gerard Boehm, Safety reviewer (combined reviews dated 1/22 and 1/25/01), Dr. Sayed Al-Habet, Office of Clinical Pharmacology and Biopharmaceutics (review dated 11/17/00), Dr. Barry Rosloff, pharmacologist (review dated 9/25/00), and Dr. Rzeszotarski, chemist (review dated 10/30/00). All reviewers recommend that the application be approved. I will briefly summarize some of the more important issues in the Approvable letter, and offer the division's recommendation for action on the application.

Clinical

Safety

We had asked the sponsor a number of questions related to the safety data. These questions fell into 2 categories: questions related to the overall presentation of the data, and questions about specific patients.

In the first group, there were a number of questions related to grouping of adverse event terms, all of which have been answered adequately. Other questions related to re-analyses of EKG data; in particular, we requested re-analyses of EKG data in patients receiving concomitant cardioactive medications. These analyses revealed a small increase in risk for some cardiovascular adverse events (mostly falls and bradycardia) in patients receiving drugs known to affect heart rate and conduction in conjunction with galantamine.

We also asked the sponsor to further evaluate the incidence of hypoglycemia (in one study, there appeared to have been a dose response for hypoglycemia). Further analyses did not reveal a dose response for hypoglycemia in the larger NDA database.

We also, in the Approvable letter, noted that there appeared to be excess mortality in the extension trials of less than 12 months duration in the patients who had been originally randomized to galantamine (GAL-GAL) compared to those who had originally randomized to placebo (PBO-GAL). We asked the sponsor to further evaluate this potential signal.

In brief, the sponsor noted that the number of deaths seen in the GAL-GAL group was not importantly different from chance (15 deaths would have been predicted, given that 63% of the exposure time was in this group, and 18 deaths were actually noted in this group). Further, the potential signal did not persist between these groups in the extension data > 12 months. For these reasons, we no longer consider this a signal of concern.

The questions pertaining to individual patients have been satisfactorily answered.

Other

The sponsor has also submitted the results of GAL-USA-11, a follow-on study to GAL-USA-10, a randomized controlled trial submitted in the original NDA. GAL-USA-11 was designed to examine the effects of withdrawal of galantamine. In this study, patients originally randomized in GAL-USA-10 to Placebo, galantamine 4 mg BID, or galantamine 8 mg BID were continued on this treatment for 6 weeks. Patients originally randomized in GAL-USA-10 to galantamine 12 mg BID were re-randomized in this study to placebo for 6 weeks. This study demonstrated that those patients in the galantamine 12 mg BID-Placebo arm had scores (ADAS-cog) after 6 weeks on placebo that approached those of the patients who continued on placebo from GAL-USA-10 (see, for example, the figure on page 21 of Dr. Mani's review). These results are consistent with the conclusion that the effect of galantamine is symptomatic, and not one on the underlying progression of the pathology of the disease.

Pharmacology

We had asked the sponsor to clarify some aspects of the mouse lymphoma assay and the CHO chromosome aberration assay. In addition, we asked the sponsor for their commitment to perform histopathologic examination of the cervixes of all animals in the rat carcinogenicity study.

Dr. Rosloff has reviewed the sponsor's responses and finds them acceptable. In particular, he now views the two assays mentioned above adequate and

negative, and the sponsor has committed to performing the histopathologic examinations requested.

CMC

The Approvable letter referred to an interim deficiency letter sent by the chemists on 6/29/00 and a DMF deficiency letter dated 3/16/00, to which the sponsor had not responded at the time of the Approvable letter. Also, the letter noted that galantamine hydrobromide had not yet been established as an official USAN name; we had asked the sponsor to respond to this.

Dr. Rzeszotarski has reviewed the sponsor's response. Although his review appears to find a number of the sponsor's responses unacceptable, he confirms, as of a discussion on 2/13/01, that these remaining issues have all been resolved. In addition, the USP has apparently permitted "galantamine" and "galantamine hydrobromide" to be covered under the tradename "Reminyl".

Biopharmaceutics

The sponsor has agreed to accept the proposed dissolution specifications.

Labeling

The review team and the sponsor have agreed to the labeling accompanying this package. The sponsor had originally proposed language in the Mechanism of Action and Clinical Trials sub-sections that the Agency did not include in our version of labeling that accompanied the Approvable letter.

Specifically, the sponsor wanted to include language referring to the drug's effect as a "nicotinic enhancer" in the Mechanism of Action Sub-section. We have rejected this language (see Dr. Rosloff's review of 9/25/00, point #3). In addition, the sponsor wanted to include a description in the Clinical Trials sub-section of several secondary measures related to overall functioning. Because these were not prospectively designated (out of a number of secondary measures assessed), and the results on these measures were not consistent (no single measure was consistently even nominally "positive" in more than one study), our Approvable labeling did not include a description of the results of these measures (see Dr. Mani's review, pages 25-30). Subsequent negotiations with the sponsor have resulted in this language being removed.

We had proposed that the sponsor create a new controlled trials Adverse Events Table; the original table pooled data from all 4 controlled trials, but 3 of the trials utilized a more rapid titration than the fourth trial; it is the titration schedule (increasing the dose every 4 weeks) from this last trial that is recommended in labeling. We had suggested that the data for the 3 rapid titration studies be presented separately from the single slow titration study. The sponsor argued

that this might encourage prescribers to utilize the more rapid titration schedule. They also noted that the relative risk of the adverse events of concern (nausea, vomiting, syncope) were about the same in the two types of trials. We agreed that the table could stay as originally proposed.

We have also added language in the Precautions and Dosage and Administration sections advising prescribers/caregivers to re-start a patient on the lowest dose (4 mg BID) and re-titrate to the maintenance dose if a patient has discontinued treatment for more than several days. This statement is analogous to the statement recently added to the labeling for Exelon, which was motivated by a case of esophageal rupture in a patient who re-started on a high dose after having been off drug. Although no such case has been reported with galantamine, there is concern that this is a risk.

The sponsor proposed a statement in the Dosage and Administration section saying that there is a suggestion that a dose of 24 mg/day might provide additional benefit for selected patients (our original proposal stated that the effective doses are 16-32 mg/day, but that there is no evidence that doses greater than 16 mg/day confer additional benefit). We have agreed to a modified version which states that there was no statistically significant difference between 24 and 16 mg/day, but that it is possible that a dose of 24 mg/day might provide additional benefit in some patients (there are increased numbers of patients who achieve 7 and 10 point differences from placebo on the ADAS-cog in the 24 mg/day group compared to the 16 mg/day group). We felt that the current version conveys a message that is supportable.

There are other, very minor, editorial changes.

RECOMMENDATION

For the reasons stated above, we recommend that the attached Approval letter be issued, with the appended labeling.

RSI 2/14/01

Russell Katz, M.D.

Cc:
NDA 21-169
HFD-120
HFD-120/Katz/Mani/Oliva/Rosloff/Racoosin/Boehm/Rzeszotarski/Guzewska
HFD-860/Al-Habet/Baweja

MEMORANDUM

DATE: July 23, 2000

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

TO: File, NDA 21-169

SUBJECT: Divisional Recommendation for Action on NDA 21-169, for the use of Reminyl (galantamine hydrobromide) in patients with Alzheimer's Disease

NDA 21-169, for the use of Reminyl (galantamine hydrobromide), an anticholinesterase inhibitor, in the treatment of patients with mild to moderate Alzheimer's Disease, was submitted by Janssen Research Foundation on 9/29/00. The application contains the results of 7 randomized controlled trials (5 performed by Janssen, 2 performed by Shire), as well as safety experience; in addition, the application contains the requisite pre-clinical, biopharmaceutic, and chemistry information.

The application has been reviewed by Dr. Ranjit Mani, of the division (efficacy review dated 6/13/00), Dr. Judy Racoosin (with the help of Drs. Gerard Boehm, Kevin Prohaska, and Michael Sevka of the division's safety team; safety review dated 7/13/00), Dr. Janusz Rzeszotarski, division chemist (reviews dated 3/16/00, 3/21/00, and 6/29/00), Dr. Barry Rosloff, division pharmacologist (review dated 5/1/00), Dr. Kun He, Division of Biometrics (review dated 6/9/00), and Dr. Al-Habet, Office of Clinical Pharmacology and Biopharmaceutics (review dated 5/19/00). The primary reviewers recommend that the application be considered Approvable. In this memo, I will briefly review the evidence submitted supporting the safety and effectiveness of the drug, and will offer the Division's recommendation for action on the NDA.

EFFICACY

As noted above, the sponsor has submitted the results of 7 controlled trials. These will be briefly discussed below.

STUDY GAL USA 1

This was a randomized, parallel group, double-blind, placebo and fixed dose response study in which patients were randomized to receive galantamine 24 mg/day, galantamine 32 mg/day, or placebo, given in a BID regimen. The primary outcomes were the ADAS-Cog and the CIBIC-Plus, the standard co-primary outcomes used in studies of symptomatic treatments for patients with AD.

The trial was 26 weeks long, with patients initially receiving 8 mg/day for one week, followed by 16 mg/day for the second week, 24 mg/day for the third –26th week, or 32 mg/day for the 4th-26th week, or placebo.

The following chart describes patient flow through the trial:

	Placebo	Gal 24mg	Gal 32 mg
Randomized	213	212	211
Completed	172	144	122
Included in ITT	207	202	197

The following table displays the results of the traditional LOCF analysis of the primary outcomes measures:

	Pla	Gal 24	Gal 32
ADAS-Cog			
Mean	27.6	23.0	24.3
Change From Baseline	2.0	-1.9	-1.4
P-value vs Pla		<0.001	<0.001
CIBIC-Plus			
Mean	4.38	4.10	4.17
P-value vs Pla		0.002	0.021

STUDY GAL INT 1

This was an identically designed trial as GAL USA 1, described above. The following chart displays patient flow in this trial:

	Placebo	Gal 24mg	Gal 32 mg
Randomized	215	220	218
Completed	186	176	163
Included in ITT	207	201	205

The following table displays the results of the traditional LOCF analysis of the primary outcomes measures:

	Pla	Gal 24	Gal 32
ADAS-Cog			
Mean	27.0	24.8	24.9
Change From Baseline	2.2	-0.6	-1.3
P-value vs Pla		<0.001	<0.001
CIBIC-Plus			
Mean	4.48	4.22	4.05
P-value vs Pla		0.015	<0.001

STUDY GAL INT 2

This was a randomized, parallel group, double-blind, placebo controlled trial in which patients were randomized to receive galantamine as a flexible dose between 24-32 mg/day, given in a BID regimen, or placebo, in a 2:1 ratio. The trial was of 12 weeks duration. The primary outcome measures were the ADAS-Cog and CIBIC-Plus. In this trial, patients received 8 mg/day for the first week, 16 mg/day for the second week, 24 mg/day for the third week, and either maintained at this latter dose or increased to 32 mg/day at the investigator's discretion, for the 4th-12th weeks.

The following chart displays patient flow in this trial:

	Placebo	Gal
Randomized	125	261
Completed	113	175
Included in ITT	120	239

The following table displays the results of the traditional LOCF analysis of the ADAS-Cog:

	Pla	Gal
ADAS-Cog		
Mean	25.0	24.7
Change From Baseline	0.6	-1.1
P-value vs Pla		<0.01

A typical LOCF analysis was not performed for the CIBIC-Plus. The protocol called for a Van Elteren test to be performed, which compared the distribution of scores in the 7 categories of the CIBIC-Plus between drug and placebo. This analysis yielded a p-value of 0.003 in favor of galantamine.

GAL USA 10

This was a multi-center, randomized, double-blind, parallel group, placebo and fixed dose response trial in which patients were randomized to receive galantamine 8 mg, 16 mg, or 24 mg/day (given as BID dosing) or placebo, in a 1:2:2:2 ratio. The trial was 21 weeks in duration. In contradistinction to the first 2 trials described, this trial evaluated a slower titration scheme.

Specifically, patients initially received 8 mg/day for the first 4 weeks. Those randomized to higher doses received 16 mg/day from weeks 5-21 (if randomized to 16 mg/day) or from weeks 5-8, if randomized to 24 mg/day, after which they received 24 mg/day from weeks 9-21. In other words, doses were increased every 4 weeks, as opposed to every week in the earlier studies.

The primary outcome measures were the ADAS-Cog and CIBIC-Plus.

The following chart displays patient flow in this trial:

	Placebo	Gal 8mg	Gal 16 mg	Gal 24 mg
Randomized	286	140	279	273
Completed	240	108	219	212
Included in ITT	255	126	253	253

The following table displays the results of the traditional LOCF analysis of the primary outcomes measures:

	Pla	Gal 8	Gal 16	Gal 24
ADAS-Cog				
Mean	30.9	28.3	27.5	27.3
Change From Baseline	1.7	0.4	-1.4	-1.4
P-value vs Pla	---	NS	<0.001	<0.001
CIBIC-Plus				
Mean	4.55	4.42	4.21	4.17
P-value vs Pla		NS	0.001	0.001

STUDY GAL 95-05

This was a randomized, double blind, parallel group, placebo controlled trial in which patients were randomized to receive either galantamine 32 mg or placebo. The trial was of 29 weeks duration; patients were treated with 8 mg/day for the first week, 16 mg/day for the second week, 24 mg/day for the third week, 28 mg/day for the fourth week, and 32 mg/day for weeks 5-29. In this trial, drug was given on a TID basis. The primary outcome measures were the ADAS-Cog, The CIBIC-Plus, and the NOSGER, the Nurses Observation Scale for Geriatric Patients.

The following chart displays patient flow in this trial:

	Placebo	Gal 32
Randomized	279	275
Completed	235	186
Included in ITT	275	267

The following table displays the results of the traditional LOCF analysis of the primary outcome measures, although this was not the protocol specified analysis:

	Pla	Gal
ADAS-Cog		
Mean	30.0	28.4
Change From Baseline	2.6	-0.3

P-value vs Pla <0.0001

The following results on the CIBIC-Plus are for the Observed Cases population; a traditional LOCF, ITT analysis was not provided for this outcome.

CIBIC-Plus

Mean	4.33	4.09
P-value vs Pla		0.034

STUDY GAL USA 5

This study was designed to assess the safety of withdrawal of galantamine. In this trial, a portion of the US patients who completed GAL INT 2 underwent a randomized withdrawal of galantamine. Patients who received placebo in INT 2 continued to receive placebo in USA 5. Patients who received either galantamine 24 or 32 mg/day in INT 2 were randomized to continue this dose or receive placebo. This trial was of 6 weeks duration, and the primary outcome was the ADAS-Cog, with the primary comparison to be the Week 6 outcome in the Pla-Pla patients compared to the Gal-Pla patients.

In this trial, 118 patients were randomized into the following sequences:

- Pla-Pla-47
- Gal-Pla-39
- Gal-Gal-32

There were no significant differences between the groups in baseline ADAS-Cog (recall that baseline in this study was also the end of GAL INT 2). The following results are reported for the Week 6 outcome (mean change in ADAS-Cog from baseline) for the traditional LOCF analysis:

Group	Mean Change in ADAS-Cog	P-value vs Pla
Pla-Pla (N=43)	0.8	
Gal-Pla (N=36)	1.4	0.67
Gal-Gal (N=30)	-1.9	0.095

GAL 93-01

This was a randomized, double blind, parallel group, placebo controlled trial in which patients were randomized to receive either galantamine 18 mg/day, 24 mg/day, 36 mg/d or placebo for 3 months, given as TID dosing. A total of 285 patients were randomized, and the primary outcome was the ADAS-Cog at Month 3.

In this study, there were no statistically significant differences between the low and high doses and placebo. The nominal p-value for the contrast between the middle dose and placebo was 0.01.

SAFETY

Exposure

Galantamine has been given to 3055 patients with Alzheimer's Disease, 2357 of whom received galantamine in controlled trials. A total of 761 patients have received daily doses of 24 mg, and about 1000 patients have received treatment for at least one year.

The total exposure to galantamine, at any dose, in controlled trials, was 802.3 patient-years, compared to 498.9 patient-years for placebo patients. Of the 802.3 galantamine patient-years, 632.2 patient-years were at daily doses of at least 24 mg, with 751.0 patient-years at daily doses of at least 16 mg.

Additionally, there was a total of 968.1 patient-years of experience in open, uncontrolled extensions to controlled trials, yielding over 1700 patient-years of experience with galantamine (at any dose) in Phase 2/3 studies.

Mortality

In controlled trials, the mortality was 2.2/100 pt-yrs in the placebo patients, and 1.7/100 pt-yrs in the galantamine treated patients. Dr. Racosin has created a table of cause-specific mortality in these trials within 30 days of the last dose (Table 10, page 23). Numbers of deaths for individual causes are small, but of some potential concern is the rate of sudden death in this cohort, which was 5/1000 pt-yrs in the galantamine treated patients (N=4) compared to a rate of 2/1000 pt-yrs in the placebo patients (N=1).

In the open extension trials of less than or equal to 12 months in duration, the mortality was 2.8/100 pt-yrs (22/778.1 pt-yrs). In this cohort, as presented by Dr. Racosin (Table 11a, page 24), the mortality was 3.5/100 pt-yrs in patients first exposed to galantamine in the controlled trials, compared to 1.7/100 pt-yrs in

patients first exposed to placebo in the controlled trials. As noted by Dr. Racoosin in Table 11b, page 25, the rate of sudden death in patient first treated with placebo was 9.9/1000 pt-yrs compared to 3.7/1000 pt-yrs for patients initially treated with galantamine.

In the open extension trials of greater than 12 months duration, the total mortality was 2.9% (5/256.3 patient-years). As presented by Dr. Racoosin (Table 12, Page 26), the mortality in patients first exposed to galantamine in controlled trials was 1.7/100 pt-yrs, compared to 2.6/pt-yrs in the patients first treated with placebo, which is in the opposite direction to the experience cited above, although the total experience is considerably less in the longer duration trials.

DISCONTINUATIONS

In controlled trials USA 1, INT 1, INT 2, 93-01, and 95-05 (the latter 2 of which used TID dosing), a total of 16% of placebo patients and 32% of galantamine treated patients discontinued treatment for any reason. A total of 8.5% of placebo patients and 26% of galantamine treated patients discontinued treatment because of adverse events. The following table displays the incidence of discontinuation by daily dose in the trials described:

Placebo	18mg (N=88)	24mg (N=488)	32mg (N=704)	36mg (N=54)	Flex (N=261)
16%	22%	18%	27%	44%	25%

In Study USA 10, in which the titration to the randomized dose was slower than in the other trials, the following discontinuation rates for adverse events were seen:

Placebo	8 mg (N=140)	16 mg (N=279)	24 mg (N=273)	Total (N=539)
7%	6%	7%	10%	8%

As is expected for this class of compounds, gastrointestinal adverse events were the most frequent type leading to discontinuation. The following events displayed a dose response for discontinuation in the US trials: nausea, vomiting, anorexia, somnolence, confusion, dizziness, asthenia, and dyspnea (taken from Dr. Racoosin's Table 13, page 28-9). In particular, the adverse event associated with discontinuation most frequently was nausea, with a 16% incidence of discontinuation at 32mg, and 10% at 24 mg (rapid titration). In general, the absolute incidence of any adverse event being responsible for discontinuation of treatment at 24 mg/day was less in USA 10 compared to the other US trials, the former of which used a slower titration (for example, the incidence of nausea

responsible for discontinuation at 24 mg in USA 10 was 4%, compared to 10% in the other US studies; similarly, the incidence of vomiting responsible for discontinuation of 24 mg dose in USA 10 was 3%, compared to 5% in the other US studies). However, the placebo rates of discontinuation for specific adverse events was also lower in USA 10 compared to the other US studies, so that the relative risk for cause specific discontinuation of the 24 mg dose in all studies was about the same.

In the open extension trials, a total of 14% of patients discontinued treatment with galantamine (227/1574) in trials of 12 months or shorter. As in the controlled trials, gastrointestinal symptoms were those most frequently responsible (see Dr. Racoosin's Table 16, page 30). There were also 5 cases of Syncope, yielding an incidence of 0.3%.

Serious Adverse Events

As can be seen in Sponsor's Table 5-12c (reproduced on page 32 of Dr. Racoosin's review), about 12% of galantamine and 11% of placebo patients treated in the controlled trials experienced a serious adverse event. The events of interest among these are listed below:

	Placebo (N=1205)	Galantamine (N=2287)
Syncope	0.6%	1.2%
Vomiting	0.2%	1.2%
Nausea	0.2%	1.0%

In general, the incidence of serious syncope was dose related in these trials (but not nausea and vomiting), including in Study USA 10, which utilized the slow titration schedule (for example, the incidence of serious syncope in this latter study was 0.7%, 1.4%, and 1.8% in the 8, 16, and 24 mg/day groups, respectively).

As noted by Dr. Racoosin, there is little information in the application that can help further elucidate the nature of the serious nausea and vomiting. She did identify a patient who had an esophageal rupture, but this occurred 18 days after discontinuing galantamine, making this likely not related to treatment.

Dr. Racoosin has evaluated the cases of syncope listed as serious. Many occurred in the setting of other events, such as concomitant medications, GI bleeds, etc. She has identified 4 cases, however, 2 with associated documented bradycardia, that cannot clearly be attributed to another cause (see her review, page 37).

In addition, though not commonly occurring, she also identified 7 patients (5 in addition to the 2 discussed above) who experienced bradycardia while on galantamine treatment. At least 3 of these additional 5 continued on treatment with no further episodes.

Other Serious Adverse Events

Renal Failure

Dr. Racoosin identified 3 patients who were described as having renal failure. In 2 of these patients, other factors seemed to be more relevant than treatment with galantamine. A third patient, a 78 year old woman, was reported to have early renal failure, but no lab results were described.

Renal-Stones

A total of 4 patients in controlled trials were reported to have had kidney stones, all on galantamine. Doses ranged from 12-32 mg/day, and the time to diagnosis of stones ranged from 6 days to 5 months after treatment initiation. Information is not complete on all 4 patients; but at least 2 appeared to have had surgery to address the problem.

Rash

Four patients were described as having had a serious rash, but information about these cases is fairly incomplete (see Dr. Racoosin's review, page 39).

Pancreatitis

Dr. Racoosin has identified 3 galantamine treated patients reported to have had pancreatitis. In 2 patients, drug treatment did not appear to be causative (1 case of stones, 1 case with a negative re-challenge), but in the last case, an 84 year old woman was hospitalized during extension treatment with galantamine, but relevant information is lacking.

Common Adverse Events

Dr. Racoosin's Table 19, page 40-41, displays the incidence of common adverse events in controlled trials. In general, 70-90% of patients reported at least one adverse event in all treatment groups. As can be seen, GI events again predominate, with nausea showing a strong dose response and vomiting showing a strong dose response in INT 1 and USA 1, but not in USA 10. Diarrhea does show a strong dose response in USA 10, however (1%, 6%, and 10% in the placebo, 16 mg, and 24 mg/day groups, respectively).

Laboratory Tests

As can be seen from Dr. Racoosin's Table 24, pages 48-9, there are no real important trends in outliers on routine laboratory tests in the controlled trials. There is a slight increase in the proportion of patients with at least one serum calcium >10.8 mg/dL (1% placebo, 2% on drug in Studies INT1 and USA 1; no such trend in USA 10), and a slight increase in the proportion of patients with at least one serum glucose of < 60 mg/dL (1.5%, 2.8%, and 4.5% of patients in placebo, 24 mg/day and 32 mg/day groups, respectively; no such trend in USA 10). There were no important mean changes between drug and placebo for any of the routine lab tests.

A total of 2 patients were noted to have LFTs >3X ULN at their last visit. The sponsor subsequently reported that these abnormalities resolved, but detailed information was not included.

One patient had a CPK of 5,463 U/L, which the sponsor reported was normal 3 weeks later; I do not have additional data on this patient.

One 85 year old woman in USA 10 had a baseline Hgb of 12.5 g/dL, which dropped to 7 g/dL at month 3. She was hospitalized and transfused, had her NSAID discontinued, and completed the study with a Hgb of 8.9 g/dL. Another 85 year old woman in this trial also experienced a drop in Hgb from 14.1 g/dL at baseline to 7.4 g/dL at month 3. Work-up revealed diverticulosis, but no evidence of bleeding. She was treated with iron, and her Hgb was 12.4 g/dL at month 5. A third patient, a 77 year old woman in an extension trial, dropped her Hgb to 7.2 g/dL from a baseline of 12.1 g/dL. She discontinued treatment and ultimately her Hgb rose to 11.5 g/dL.

EKG/Cardiac Intervals/Heart Rate

In addition to EKGs monitored in other clinical trials, the sponsor performed Study GAL USA 16, a 6 week study in which 139 patients were randomized to placebo (N=69) or galantamine (N=70) at a maximally tolerated dose up to 32 mg/day. Patients received Holter monitoring at baseline, and every 2 weeks. Treatment was initiated at 8 mg/day for the first week, 16 mg/day during Week 2, 24 mg/day during Weeks 3 and 4, and 32 mg/day during Weeks 5 and 6, if tolerated.

In this study, patients receiving galantamine had, on average, a 2-3 bpm decrease in heart rate, compared to a small increase in the placebo patients. This was consistent with the results of EKG monitoring in the controlled trials, in which galantamine patients experienced an average decrease in heart rate of about 3-4 bpm compared to a decrease of 1 bpm in the placebo patients.

In the controlled trials, the incidence of bradycardia recorded as an adverse event was about 2-3%, which ranged from 2-10 times greater than in the placebo

group (depending upon which studies are included in this comparison). The rate of bradycardia reported as an adverse event in the extension trials ranged from 1-5%. There were few discontinuations for bradycardia, and few bradycardia events categorized as serious (see above).

In Study GAL USA 16, there was a 9% incidence of first degree AV block in galantamine patients compared to a 6% incidence in placebo patients. There was a 3% incidence of third degree AV block compared to 0% in the placebo patients. Consistent with these findings, there was a dose related increase in the mean difference in change from baseline in PR interval between the galantamine and placebo patients: a difference of 2.7 msec at Week 2, 4.0 msec at Week 4, and 5.2 msec at Week 6.

In the controlled trials, there was a mean increase of the PR interval of 3.4 msec in the 32 mg/day group compared to an increase of 0.7 msec in the placebo group (0.4 msec increase for the 24 mg group). There was also an increase in the proportion of patients who experienced at least one episode of a PR interval >210 msec in the 32 mg/day group (4%) compared to the placebo patients (2%). In Study USA 10, there was a negative dose response for mean increase in PR interval, so that the 8 mg/day group had an increase of 4.2 msec, and the 24 mg/day group had an increase of 2.7 msec, compared to a 2 msec increase in the placebo patients.

There was also an excess in the incidence of first degree AV block reported as an adverse event in the controlled trials in galantamine treated patients compared to placebo patients.

There were no important changes in the QTc intervals.

Blood Pressure

In controlled trials, there was a decrease in both systolic and diastolic blood pressure of about 2-10 mm Hg. About 2% of galantamine treated patients reached criteria for clinically relevant decreases in either SBP or DBP.

In trials INT 1 and USA 1, the incidence of syncope was dose related, with a rate of 1.1%, 1.4%, and 3% in the placebo, 24 mg/day, and 32 mg/day groups, respectively. In USA 10, the incidence was 0.7%, 2.2%, and 3.3% in the placebo, 24 mg/day, and 32 mg/day groups, respectively.

COMMENTS

The sponsor has submitted the results of 3 randomized controlled trials of approximately 6 months duration which evaluate the effectiveness of daily doses of 8-32 mg, given as BID dosing (GAL INT 1, GAL USA 1, GAL USA 10). Study GAL USA 10 differs from the first 2 studies in that it was 5 months long, used a

slower titration schedule (dose increased every month by 8 mg/day, instead of every week), and studied lower doses (8, 16, and 24 mg/day compared to 24 and 32 mg/day). In addition, they have submitted the results of 2, 12 week studies, one of which evaluated BID dosing (GAL IINT 2), and one of which evaluated TID dosing (GAL 93-01). They have also submitted the results of a 6 month trial evaluating TID dosing, and a 6 week trial designed to evaluate the effects of drug withdrawal.

The trials enrolled the typical type of patients (MMSE range of about 11-24) that have been evaluated in previous NDAs for cholinesterase inhibitors. The 3 RCTs that evaluated BID dosing over 5-6 months (GAL INT 1, GAL USA 1, GAL USA 10) all have demonstrated significant effects of the drug compared to placebo on the "traditional" primary outcomes of ADAS-Cog and CIBIC-Plus, and, therefore, effectiveness of galantamine as a symptomatic treatment of patients with mild-moderate Alzheimer's Disease has been demonstrated. It is interesting to note that the results of GAL USA 5, the trial in which patients underwent a randomized withdrawal maneuver, supports the view that the treatment is symptomatic, given that when patients who had received galantamine were re-randomized to placebo, their ADAS-Cog scores approached those of the patients who had been on continuous placebo.

The current data support the effectiveness of daily doses of 16-32 mg, but do not distinguish any important differences between these doses. Further, because there was no direct comparison of the effects of the "fast" and "slow" titration schedules (GAL USA 1 and GAL INT 1; GAL USA 10, respectively), we cannot draw any conclusions about the relative effectiveness of the drug when given by these 2 different titration schemes.

Galantamine has been reasonably well tolerated in patients with Alzheimer's Disease. It is associated with the panoply of adverse events seen in association with the use of other cholinesterase inhibitors, including predominantly nausea and vomiting, but also decrease in heart rate, first degree AV block, decreases in systolic and diastolic blood pressure, and syncope. None of these events has been seen frequently, and there were few of these events reported as serious, or responsible for drug discontinuation.

There were no important systematic changes seen in routine blood test monitoring.

Dr. Racoosin has made some interesting observations about the mortality data in the NDA. While there is no difference in mortality between drug and placebo treated patients in the controlled trials (indeed, the mortality is numerically worse in the placebo group), the analyses of cause-specific mortality in the controlled trials reveals a relative risk of about 2.5 for the cause "sudden death" in patients who received galantamine compared to placebo treated patients. Further, an analysis of the uncontrolled extension data reveals a risk of mortality of about 2.6

deaths/100 pt-yrs, compared to a risk of 1.7 deaths/100 pt-yrs in the controlled trials, raising the possibility that increased exposure is related to increased mortality.

In addition, Dr. Racoosin notes that an analysis of the patients in the extension trials by their original treatment assignment in the controlled trials (placebo or galantamine) reveals increased mortality in the patients originally randomized to galantamine compared to those originally randomized to placebo (3.1 vs 1.6 deaths/100 pt-yrs, respectively), again raising the possibility that mortality is related to prolonged treatment with galantamine. In the extension cohort, the analysis of cause specific mortality revealed an increase in the rate of sudden death in the patients originally randomized to placebo compared to those originally randomized to galantamine (9.9 vs 3.7 deaths/1000 pt-yrs; relative risk of about 2.7).

Although, as Dr. Racoosin suggests, we will ask for additional information to help us attempt to definitively address this question, my view is that there is not a strong signal of increased mortality in the database. Critically, there is no finding of increased mortality in the controlled trial database, a database of some considerable size. This is the most reliable evidence we have on this question. The identification of increased mortality due to sudden death in the controlled trials is interesting, but entirely retrospective, of course, the numbers are small, and examination of the individual causes of mortality in the RCTs reveals several causes for which there is an increased relative risk for placebo (although I agree that sudden death is, generically, perhaps of more interest with this class of compounds).

The increased relative risk of sudden death in the extension studies in the patients initially treated with placebo compared to those originally treated with galantamine raises the possibility that patients newly treated with galantamine are at increased risk for this event, but sudden death was seen at varying times after initiation of treatment, including many months later (suggesting to me that this is not an immediate phenomenon, as might be expected if the drug truly caused sudden death in "newly" treated patients), and, as Dr. Racoosin notes (page 82), the patients in the extension who were originally treated with galantamine actually had the greater incidence of discontinuation due to bradycardia, which, if the mechanisms of conduction abnormalities and sudden death are linked, is not consistent with the original observation.

Finally, the increased rate of mortality in the open extension experience compared to that in the controlled trials and the increased mortality in patients originally treated with galantamine compared to those originally treated with placebo may each be the result of numerous factors, as discussed in detail by Dr. Racoosin (pages 80-81). In my view, these isolated findings do not present a consistent picture of a particular concern regarding mortality. However, they cannot be dismissed completely, given the drug's capacity to affect cardiac

conduction, heart rate, and blood pressure (including causing syncope). I do believe, though, that labeling can adequately describe and discuss these events.

There have been several reports of serious events, including rash, renal failure, pancreatitis, and liver injury. For some of these reports, the sponsor did not provide sufficient information to permit an adequate review, and we will ask for this additional information.

Finally, there are several comments from the OCPB, CMC, and Pharmacology reviewers that need to be transmitted to the sponsor:

RECOMMENDATION

The attached Approvable letter should be issued.

/s/

Russell Katz, M.D.

Cc:

NDA 21-169

HFD-120

HFD-120/Katz/Mani/Racoosin/Boehm/Prohaska/Sevka/Fanari/Rosloff/Fitzgerald

HFD-120/Rzeszotarski/Guzewska

HFD-860/AI-Habet/Baweja

HFD-710/He/Jin/Chi

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED:

October 22, 1999

DUE DATE:

July 29, 2000

OPDRA CONSULT #: 99-072

TO:

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

THROUGH:

Project Manager
Division of Neuropharmacological Drug Products
HFD-120

PRODUCT NAME:

Reminyl (Galantamine Tablets)
4 mg, 8 mg and 12 mg

MANUFACTURER:

Janssen Pharmaceutica Inc.

NDA #: 21-169

SAFETY EVALUATOR: Carol Holquist

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name Reminyl. This is considered a tentative decision and the firm should be notified that this name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward. The firm could be asked to submit information in its periodic safety updates, in which the firm will provide the names of all FDA approved drug names from 2/3/2000 and certify that this name does not sound-alike or look-alike to those names.



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Food and Drug Administration