

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-615**

**Administrative/Correspondence Reviews**

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> March 1, 2005	<b>DESIRED COMPLETION DATE:</b> April 1, 2005	<b>ODS CONSULT #:</b> 05-0039-1
<b>TO:</b> Russell Katz, M.D. Director, Division of Neuropharmacological Drug Products HFD-120		
<b>THROUGH:</b> Melina Griffis, R.Ph. Project Manager, Division of Neuropharmacological Drug Products HFD-120		
<b>PRODUCT NAME:</b> <b>NDA 21-169: Razadyne</b> (Galantamine Hydrobromide) Tablets, 4 mg, 8 mg, 12 mg (base) <b>NDA 21-224: Razadyne</b> (Galantamine Hydrobromide) Oral Solution, 4 mg/mL <b>NDA 21-615: Razadyne</b> (Galantamine Hydrobromide) ER Extended- release Capsules, 8 mg, 16 mg, 24 mg (base)		<b>NDA SPONSOR:</b> Johnson and Johnson Pharmaceutical Research and Development, L.L.C.
<b>SAFETY EVALUATOR:</b> Kimberly Culley, RPh		
<b>RECOMMENDATIONS:</b>  1. DMETS has no objections to the use of the proprietary name Razadyne/Razadyne ER from a safety perspective. However, DMETS would like to recommend that the sponsor provide adequate education for healthcare providers of the availability of the extended-release product and the name change from Reminyl to Razadyne with launch of the product.  2. DDMAC does not object to the name Razadyne from a promotional perspective.		
		
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Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

\*\*\*NOTE: This review contains proprietary and confidential information that should not be released to the public.\*\*\*

**DATE OF REVIEW:** March 24, 2005

**NDA HOLDER:** Johnson and Johnson, Pharmaceutical Research and Development, L.L.C.

NDA Number	Established Name and Product Strengths	Proposed Proprietary Name
21-615	Galantamine Hydrobromide Extended-release Capsules, 8 mg, 16 mg, 24 mg (base)	Razadyne ER Extended-release Capsules
21-169	Galantamine Hydrobromide Tablets 4 mg, 8 mg, 12 mg (base)	Razadyne Tablets
21-224	Galantamine Hydrobromide Oral Solution, 4 mg/mL	Razadyne Oral Solution

**I. INTRODUCTION:**

In a review dated July 29, 2004, DMETS recommended against the use of the proposed proprietary name Reminyl ER for the new dosage form for the marketed product Reminyl (NDA 21-615). From that review, DMETS also recommended that consideration be given to changing the proprietary name of the immediate-release Reminyl products due to confusion between Reminyl and Amaryl found in post-marketing medication error reports reviewed. At that time, Johnson and Johnson marketed Reminyl in an immediate-release tablet formulation in 4 mg, 8 mg, and 12 mg strengths and an oral solution in a concentration of 4 mg per milliliter under NDA 21-169 and NDA 21-224 respectively. In the sponsor's correspondence dated December 17, 2004, reference is made to a November 10<sup>th</sup> teleconference where FDA and J&JPRD agreed that with the pending approval of the extended-release formulation of galantamine hydrobromide, a name change from Reminyl would be appropriate. Also in response to confusion between Reminyl and Amaryl, the sponsor has devised a risk management plan which includes "Dear Healthcare Professional" and "Dear Pharmacist" letters, a Press Release, a "Sales Force Visual Fact Sheet", journal ads, and a "Caregiver Awareness Brochure". The risk management plan also provides web sites for information and medication error reporting, studies conducted by [redacted] and Med-E.R.R.S., and a healthcare provider support program called "Sharing Care". Although DMETS is involved in the review of the risk management plan, it will not be the subject of this name review. In a review dated December 29, 2004, DMETS recommended against the use of the proposed names [redacted] due to concerns relating to look-alike and/or sound-alike confusion with Riomet and Remeron. Additionally, DMETS recommended against the use of the proposed names [redacted] due to concerns relating to look-alike and/or sound-alike confusion with Remeron. On March 1, 2005, the Division forwarded a consult for the proposed names [redacted] and Razadyne/Razadyne ER for review by DMETS. The consult also included a study conducted by [redacted] in support of [redacted]. In ODS consult 05-0039, DMETS found the names [redacted] unacceptable due to potential confusion with Optivar and Opticrom. The following review is for the proposed proprietary names Razadyne/Razadyne ER.

## PRODUCT INFORMATION

Razadyne is the proposed name to replace Reminyl in the marketplace. Reminyl contains galantamine hydrobromide, which is a reversible, competitive acetylcholinesterase inhibitor for the treatment of mild to moderate dementia of the Alzheimer's type. Currently, Reminyl is available as two formulations, tablet and oral solution. The tablets are 4 mg, 8 mg and 12 mg with the solution as a 4 mg/mL concentration. The tablets should not be crushed or chewed during administration. The dosing for the tablets is a starting dose 4 mg twice daily with a maintenance dose of 8 mg twice daily. The tablets are packaged in bottles of sixty with the solution in 100 mL bottles with a calibrated pipette. Razadyne ER will be the extended-release capsule available as 8 mg, 16 mg and 24 mg strengths. The dosage range for Razadyne ER is 16 mg to 32 mg (base) given in a dosing interval of once daily with food. Razadyne will be supplied in bottles of 30 and 300 capsules.

## **II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2,3</sup> as well as several FDA databases<sup>4</sup> for existing drug names which sound-alike or look-alike to Razadyne to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>5</sup>. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### **A. EXPERT PANEL DISCUSSION (EPD)**

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names Razadyne and Razadyne ER. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical, other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC does not object to the name Razadyne from a promotional perspective
2. The Expert Panel identified three proprietary names and one established name (trazodone, Regitine, Tazidime and [ \_ \_ \_ ] that were thought to have the

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<sup>1</sup> MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

<sup>4</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

<sup>5</sup> WWW location <http://tess2.uspto.gov/bin/gate.exe?f=searchstr&state=m2pu5u.1.1>

\*\*\* Proprietary and confidential information that should not be released to the public.

potential for confusion with Razadyne. Additionally, the remaining six names (Visudyne, Normodyne, Reyataz, Neptazane, Naprosyn and Nizatidine) were identified by independent review. These ten products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names for Razadyne Identified by DMETS Expert Panel and Independent Review

Product Name	Established name, Dosage Form(s), Strength(s), How supplied (if applicable)	Usual adult dose*	Other**
Razadyne ER Capsules	Galantamine Hydrobromide Extended-release Capsules, 8 mg, 16 mg, and 24 mg (base)	Take 1 capsule once daily.	
Razadyne Tablets	Galantamine Hydrobromide Tablets, 4 mg, 8 mg, 12 mg (base)	Take one tablet two times daily.	
Razadyne Oral Solution	Galantamine Hydrobromide Oral Solution, 4 mg/mL	Take one milliliter two times daily. May increase to 24 mg per day in two divided doses.	
Trazodone	Trazodone Tablets: 50 mg, 100 mg, 150 mg, 300 mg	150 mg per day in divided doses, may be increased by 50 mg per day every 3 to 4 days	LA/SA
Regitine	Phentolamine Mesylate, 5 mg vial	5 -10 mg within 12 hours	LA/SA
Tazidime	Ceftazidime Powder for Injection 500 mg, 1 gram, 2 gram, 6 gram	250 mg to 2 grams every 8-12 hours Pseudomonal Lung infections: 30-50 mg/kg every 8 hours Pediatric: 30-50 mg/kg every 8 hours	LA/SA
[			
Visudyne	Verteporfin Lyophilized cake for Injection, 15 mg reconstituted to 2 mg/mL	6 mg/m <sup>2</sup> infused over 10 minutes	LA/SA
Normodyne	Labetolol Hydrochloride Tablets: 100 mg, 200 mg, 300 mg Injection: 5 mg/mL	Oral: Initial dose: 100 mg twice daily, Maintenance dose: 200- 400 mg twice daily. Intravenous: Initial 20 mg (0.25 mg/kg), then 40 mg-80 mg until desired effect.	LA
Reyataz	Atazanavir Sulfate, 100 mg, 150 mg and 200 mg	400 mg daily	LA
Neptazane	Methazolamide Tablet: 25 mg, 50 mg	Adults: 50 to 100 mg orally 2 to 3 times per day. May be used temporarily or for continuous treatment.	LA
Naprosyn	Naproxen Tablets: 250 mg, 375 mg, 500 mg Suspension: 125 mg/5 mL	250 mg ,375 mg, 500 mg twice daily  Suspension for juvenile arthritis: 10 mg/kg in 2 divided doses.	LA

Product Name	Established name, Dosage Form(s), Strength(s), How supplied (if applicable)	Usual adult dose*	Other**
Razadyne ER Capsules	Galantamine Hydrobromide Extended-release Capsules, 8 mg, 16 mg, and 24 mg (base)	Take 1 capsule once daily.	
Razadyne Tablets	Galantamine Hydrobromide Tablets, 4 mg, 8 mg, 12 mg (base)	Take one tablet two times daily.	
Razadyne Oral Solution	Galantamine Hydrobromide Oral Solution, 4 mg/mL	Take one milliliter two times daily. May increase to 24 mg per day in two divided doses.	
Nizatidine	Nizatidine Tablets (otc): 75 mg Capsules: 150 mg and 300 mg Oral Solution: 150 mg/mL	150 mg to 300 mg daily (may be in divided doses)	LA

\*Frequently used, not all-inclusive.  
\*\*L/A (look-alike), S/A (sound-alike)  
\*\*\* Proprietary and confidential information that should not be released to the public

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Razadyne/Razadyne ER were discussed by the Expert Panel.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Razadyne with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Outpatient prescriptions and an inpatient order were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Razadyne (see page 6). These prescriptions were optically scanned and one prescription was delivered to a random sample of participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice-mail and sent to a random sample of participating health professionals for their interpretation and review. After receiving either written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> <p>Razadyne 4mg  <math>\frac{1}{2}</math> po bid            #30</p>	<p>Razadyne 4 mg            number 30            one twice a day</p>
<p>Inpatient RX:</p> <p><del>Razadyne 4 mg po bid #30</del>  <del>Razadyne 4 mg po bid #30</del></p>	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

The root name Razadyne as it appears in the immediate-release tablet and oral solution, as well as the extended-release product are the subject of this proprietary name review. In reviewing the proprietary name Razadyne/Razadyne ER, the primary concerns related to look-alike and sound-alike confusion with Trazodone, Regitine, Tazidime, [ ] Visudyne, Normodyne, Reyataz, Neptazane, Naprosyn and Nizatidine.

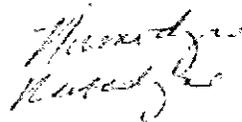
Reminyl and Amaryl were also included in the risk assessment because of the name change from Reminyl to Razadyne and, by extension, the similarities and postmarketing confusion between Reminyl and Amaryl. DMETS did not identify any phonetic or orthographic similarities between Razadyne and Amaryl. Although the names Razadyne and Reminyl share the first letter "R", the remainder of each name is phonetically and orthographically unique. The down stroke of the "z" and upstroke of the "d" in Razadyne should serve to distinguish these names orthographically from Amaryl and Reminyl.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Razadyne.

1. Look-alike and Sound-Alike Similarities

- a. Normodyne may look similar to Razadyne when scripted. Normodyne is labetalol in a tablet and injectable form for the treatment of hypertension. Currently, Schering does not market the brand of Normodyne, but generics continue to be produced. Thus, since Normodyne is a well known brand name, labetalol may be dispensed for a prescription written as Normodyne. Labetalol is available in 100 mg, 200 mg and 300 mg tablets and 5 mg/mL injection. The recommended initial dose is 100 mg twice daily, which may be increased by 100 mg increments to achieve control. The recommended maintenance dose is 200 to 400 mg twice daily. Initial parenteral

dosing is 20 mg, injected slowly over 2 minutes; additional injections of 40-80 mg may be given at 10 minute intervals. For slow continuous infusion, add 200 mg to 160 mL of IV fluid to prepare 1mg/mL solution at a rate of 2 mL/min (2 mg/min) or add 200 mg to 250 mL of an IV fluid to prepare 2 mg/3 mL solution; given at a rate of 3 mL/min (2 mg/min). Adjust infusion rate according to BP response with the effective cumulative intravenous dose of 50 to 200 mg, up to 300 mg. The orthographic similarities stem from identical endings of “-dyne”, likeness of the central “o” and “a” and the potential of “n” and “r” to appear alike when leading a word. Furthermore, the “z” of Razadyne may look like the “r” of Normodyne when printed, not scripted.

Handwritten text showing the words 'Razadyne' and 'Normodyne' written in cursive. The 'z' in Razadyne and the 'r' in Normodyne are written in a way that makes them look very similar, illustrating the potential for confusion when the words are not printed.

The products share the characteristics of route of administration (oral), dosing frequency (twice daily), and duration of treatment (maintenance). However, they differ in product strength (100 mg, 200 mg and 300 mg compared to 4 mg, 8 mg, 12 mg, 16 mg and 24 mg). The only potential confusion for dosing overlap would involve the parenteral administration of labetalol, since on initial infusion the patient may receive 40 to 80 mg for hypertension control. Upon scripting, this may be confused with the 4 mg and 8 mg strengths of Razadyne; however, the order for labetalol will probably be written as a starting dose with the allowed incremental increases for control (i.e. 20 mg to be followed by 40 mg every 10 mins until systolic is 150). In addition, orders for injectable labetalol will be mainly ordered in a setting where the route of administration will be indicated on the order. Since the order process for the parenteral administration will be distinct, confusion should be minimal. Due to the differing strengths, DMETS believes confusion between Normodyne and Razadyne will be minimal.

- b. Reyataz may look similar to Razadyne when scripted. Reyataz contains atazanavir sulfate in 100 mg, 150 mg and 200 mg capsules for the treatment of HIV-1 infection. The recommended dose is 400 mg once daily with food for therapy naïve patients and 300 mg once daily with 100 mg ritonavir for experienced patients. The orthographic similarities stem from the shared leading “R” with the identical placement of the downstroke (“y” of Reyataz compared to “z” of Razadyne) and upstroke (“t” of Reyataz and “d” of Razadyne). In addition, the concluding “z” of Reyataz if scripted using a downstroke may serve as another similarity since it is a downstroke at the end of the name (similar to Razadyne). However, this would require the reader to disregard the lack of the “ne” or the existence of the “ne” on the end of the name. DMETS doubts this would happen, but it is not uncommon to “trail” ending letters of words; thus obscuring the ending for comprehension.

Handwritten text showing the words 'Reyataz' and 'Razadyne' written in cursive. The 'y' in Reyataz and the 'z' in Razadyne are written in a way that makes them look very similar, illustrating the potential for confusion when the words are not printed.

The products share the characteristics of route of administration (oral), dosing frequency (daily with the Razadyne ER), and duration of treatment (maintenance therapy). However, they differ in product strength (100 mg, 150 mg and 200 mg compared to 4 mg, 8 mg, 12 mg, 16 mg and 24 mg) and dosing frequency of the immediate release product (twice daily). Due to the differing strengths and dosing frequency, the possibility for confusion is regarded to be low.

- c. Trazodone may look and sound similar to Razadyne when scripted and spoken. Trazodone is available as 50 mg, 100 mg, 150 mg and 300 mg tablets for the treatment of depression. Trazodone should be initiated at a low dose with gradual increases. The recommended dose is 150 mg per day in divided doses, which may be increased 50 mg per day every three to four days. The maximum dose should not exceed 400 mg per day in divided doses for outpatients and 600 mg per day in divided doses for inpatients. The orthographic similarities stem from the central "zod" of trazodone and "zad" of Razadyne which appear identical when scripted, which is compounded by the possibility for the leading "T" and "R" to appear alike. However, the downstroke of the "y" of Razadyne should serve as a distinct characteristic in scripting. The phonetic similarities route in the shared central "z" that is powerful in speech, followed by the "d" and "n." The concluding "dyne" and "done" should serve to distinguish the names in speech; since this would allow for the misinterpretation/dropping of the leading "t" of trazodone.

*Trazodone vs Razadyne*

The products share the characteristics of route of administration (oral), dosing regimen (one twice daily), and duration of treatment (maintenance therapy). However, a primary difference that will create distinction is the strength (50 mg, 100 mg, 150 mg and 300 mg compared to 4 mg, 8 mg, 12 mg, 16 mg and 24 mg). Therefore, DMETS believes the possibility for confusion to be minimal.

- d. Regitine may look and sound similar to Razadyne when scripted and spoken. Regitine contains phentolamine mesylate as a 5 mg powder for injection for the treatment of pheochromocytoma (to prevent or control hypertensive episodes) and dermal necrosis (to prevent and treat the sloughing following intravenous administration or extravasation of norepinephrine or dopamine). The proprietary name of Regitine does not appear available in the U.S. market, but the name is well known in medicine. Thus, prescriptions may be written for Regitine and the order completed with the generic, phentolamine. For control of hypertension, 5 mg for adults and 1 mg for children is injected intravenously or intramuscularly one to two hours before surgery; the same amount may be administered during surgery for hypertension control. For prevention of dermal necrosis, ten milligrams are added to each solution containing norepinephrine. For treatment, five to ten milligrams in 10 mL of saline for adults and 0.1 to 0.2 mg per kilogram for children are injected into the extravasation area. The orthographic similarities stem from the shared leading "R", which is compounded by the downstroke ("g" and "z"), and upstroke ("t" and "d") in the same placement in the name. However, the downstroke of the "y" in Razadyne should serve as a distinguishing characteristic. The phonetic similarities route in the shared three syllable count and leading "R"; plus the possibility for "ine" and "yne" to be pronounced as "in" as in the word "incline." However, the "g" of Regitine and the "z" of Razadyne should help to distinguish the two in speech.

There is one possibility for characteristic overlap between the names, which involves a child of 20 to 40 kilogram that would receive 4 mg for extravasation. However, due to the context of use and the fact that Razadyne will be administered in a more aged population, the possibility for confusion is low. The products share no further characteristics as shown by the following: dosage form (injectable compared to tablet), route of administration (intravenous compared to oral), strength (5 mg compared to 4

mg, 8 mg, 12 mg, 16 mg and 24 mg), dosing frequency (one time treatment with possibility for a repeat compared to once or twice daily), duration of treatment (one time therapy compared to maintenance), and context of use (in hospital for pheochromocytoma, a rare condition compared to therapy for Alzheimer's disease, primarily outpatient). Therefore, DMETS believes the possibility for confusion is minimal.

- e. Tazidime may look and sound like Razadyne when scripted and spoken. Tazidime was a proprietary name for ceftazidime. Tazidime has been discontinued by Eli Lilly, but the proprietary name is well established and still can be found in reference texts. Thus, prescriptions may be written for Tazidime and filled with Ceptaz, Tazicef, Fortaz, or a generic product. Ceftazidime is available in the following strengths 500 mg, 1 gram, 2 grams as powder for injection and 1 gram and 2 gram as premixed injection. Ceftazidime is used in the treatment of lower respiratory tract infections, skin and skin structure infections, urinary tract infections, bacterial septicemia, bone and joint infections, gynecological infections, intra-abdominal infections, and CNS infections. The recommended dose for adults ranges from 250 mg to 2 gram intravenously or intramuscularly every 8 to 12 hours. For pseudomonas lung infections in cystic fibrosis patients, the dose is 30 to 50 mg per kilogram intravenously every 8 hours (neonates 30 mg every 12 hours).

*Tazidime*  
*Razadyne*

The products share no characteristics as shown by the following: dosage form (injectable compared to tablet), route of administration (intravenous compared to oral), strength (500 mg, 1 gram, 2 gram compared to 4 mg, 8 mg, 12 mg, 16 mg and 24 mg), dose (250 mg to 2 grams and 30 mg to 50 mg compared to 4 mg, 8 mg, 12 mg, 16 mg and 24 mg), dosing frequency (every 8 hours and every 12 hours compared to BID), duration of treatment (short course for infection compared to maintenance), and context of use (in hospital use for treatment of infection compared to therapy for Alzheimer's, primarily outpatient). Therefore, DMETS believes the possibility for confusion is minimal.

- f. [

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- g. Visudyne may look and sound like Razadyne when scripted and spoken. Visudyne contains verteporfin as a 15 mg lyophilized cake for injection. Once reconstituted, the strength is 2 mg per milliliter and the product must be protected from light and used within 4 hours. The recommended dose is 6 mg/m<sup>2</sup> to be infused over 10 minutes. Visudyne is indicated for the treatment of predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis. A course of therapy is a two-step process requiring administration of both drug and light. The orthographic and phonetic similarities stem from the shared ending of “-dyne.” Orthographically, this is compounded by the possibility for the leading “V” compared to “R” and “s” compared to “z” to appear alike. This correlates to the phonetic similarity that involves the shared sound of “s” with the “z.” However, in speech, the leading “V” and “R” should help to distinguish between the names.

Although there is the potential for confusion with the 6 mg/m<sup>2</sup> strength compared to the 16 mg strength of Razadyne, most orders will be calculated for the patient, which leads to a potential for dose overlap of 12 mg for Visudyne and Razadyne. However, this leads to the differences in context of use. Visudyne is a specialized therapy to be used by an ophthalmologist in conjunction with light therapy. The ophthalmologist or his/her staff should be directly involved with the reconstitution and administration of the product, which creates another method to alleviate confusion. In addition, it

appears that physicians order directly from two distributors; thus eliminating confusion in the pharmacy. Furthermore, the products share no further characteristics as shown by the following: dosage form (injectable compared to tablet), route of administration (intravenous compared to oral), dosing frequency (one time use compared to daily/twice daily), duration of treatment (one time therapy compared to maintenance treatment), context of use (specialized procedure involving light therapy compared to daily oral dosing) and indication of use (macular degeneration compared to Alzheimer's disease). Due to limited distribution, DMETS believes the possibility for confusion is minimal.

- h. Neptazane may look similar to Razadyne when scripted. Neptazane contains methazolamide as 25 mg and 50 mg tablets as an adjunctive treatment of open-angle or secondary glaucoma or for short-term treatment of narrow-angle glaucoma when delay of surgery is desired. The recommended dose is 50 to 100 mg two to three times daily. Although the proprietary name product of Neptazane is no longer marketed, this name is well known in medicine and generic products are available. Thus, practitioners may write a prescription for Neptazane and it can be filled with a generic methazolamide. The orthographic similarities stem from the similarly placed upstrokes and downstrokes (see below) and the possibility for a capitalized "N" and "R" to appear identical when scripted. In addition, both names conclude with "ne."

Neptazane    Green: downstroke, Purple: upstroke and Red: downstroke  
Razadyne

The products share the characteristics of route of administration (oral), dosing frequency (two times daily), duration of therapy (maintenance), and dosage form (tablet). However, the products differ in strength (25 mg and 50 mg compared to 4 mg, 8 mg, 12 mg, 16 mg and 24 mg) and prescribed dose (50 to 100 mg compared to 4 mg, 8 mg, 12 mg, 16 mg and 24 mg). Although consideration should be given to the possible confusion with the 25 mg of Neptazane and 24 mg of Razadyne; the dosing frequency would differ (two to three times daily compared with daily) and the 24 mg of Razadyne should be noted with the modifier of ER. Furthermore, the usual dose of Neptazane is 50 mg, which would imply the directions for use would be "2 tablets"; thus creating another cue for correct identification of the drug name. The difference in strength, dose and frequency of dosing should help to minimize the potential for confusion between the two drug products.

- i. Naprosyn may look similar to Razadyne when scripted. Naprosyn contains naproxen in 250 mg, 375 mg and 500 mg tablets and 125 mg per 5 milliliter suspension for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and juvenile arthritis. The recommended dose is 250 mg, 375 mg or 500 mg twice daily and 10 mg per kilogram in 2 divided doses for the treatment of juvenile arthritis. The orthographic similarities stem from the shared "yn" in similar positioning compounded by the downstrokes of "p" compared to "z" in the same position. This is only enhanced by the possibility for a leading "N" and "R" to appear similar (see below). However, the upstroke of the "d" in Razadyne should serve to distinguish between the two names.



The products overlap in route of administration (oral), dosing frequency (two times daily), duration of therapy (maintenance), and dosage form (tablet). However, the products differ in strength and prescribed dose (125 mg (per 5 mL), 250 mg, 375 mg and 500 mg compared to 4 mg, 8 mg, 12 mg, 16 mg and 24 mg). Consideration must be given to the possibility for overlap in the two solutions available for both drug products. Naprosyn is available as a 125 milligram per 5 milliliter solution compared to the 4 milligram per milliliter Razadyne solution. The recommended dosing indicates the solution would rarely be dosed lower than 5 mL or one teaspoonful; where Razadyne will be dosed in increments of single milliliters. Thus, the difference in dosing volume should create another method of identification. If confusion or question was raised or if the practitioner assumes the prescription was Razadyne, the calibrated dosing pipette of Razadyne may help with proper identification. The pipette is calibrated to 4 mL, which would produce questions if the prescription is written for one teaspoonful or higher. Thus, the difference in strength and dose should help to minimize the potential for confusion between the two drug products.

- j. Nizatidine may look similar to Razadyne when scripted. Nizatidine is the established name for Axid. Nizatidine is available in 150 mg, 300 mg capsules (75 mg Axid SR is over-the-counter) and 15 mg/mL oral solution for the treatment of duodenal ulcer, benign gastric ulcer, gastroesophageal reflux disease and heartburn (otc). The recommended dose is from 150 mg daily to 300 mg daily or in divided doses. The orthographic similarities stem from the shared "z" and "d" with similar placement in the name. This is compounded by the possible likeness of the leading "R" and "N" and the tendency for all vowels to appear similar when encompassed in a name (see below). However, the "ti" of Nizatidine does provide a distinguishing mark for identification and also serve to lengthen the name.



The products share the following characteristics route of administration (oral), dosing frequency (daily and two times daily), and duration of therapy (maintenance). However, the products differ in strength and prescribed dose (75 mg, 150 mg and 300 mg compared to 4 mg, 8 mg, 12 mg, 16 mg and 24 mg). Both products are available as oral solutions, with Nizatidine at 15 mg/mL and Razadyne at 4 mg/mL. This should not result in confusion, since Nizatidine is not recommended for children under the age of twelve with a dose of 2 teaspoonfuls or 10 mL twice daily. Thus, the dosing for Razadyne would be too low for confusion with Nizatidine and the dose for Nizatidine much too high for Razadyne. If confusion were to occur, Razadyne is packaged with a pipette only calibrated to 4 mL, which also serves as a cue for correct dosing/name identification. The difference in strength and dose should help to minimize the potential for confusion between the two drug products.

2. INDEPENDENT NAME ANALYSIS [ ]

The sponsor contracted with the [ ] to conduct a study which included the name candidate, Razadyne. The study was conducted for a proposed [ ]

[ ] . A review has not been conducted for Razadyne to be the proprietary name for galantamine hydrochloride. The full [ ] proprietary name assessments for Razadyne and Razadyne ER were not provided.

[ ] reported that the proposed proprietary name received a favorable safety evaluation [ ] . One of the two dated pieces provided was that Razadyne was not misinterpreted for any existing brand/generic drug name in either the verbal or handwritten prescription studies in either indication. The last noted that none of the medical professionals in either study identified any notable potential exaggerative, misleading, or inappropriate claims with Razadyne. [ ] overall found the research conducted for [ ] to support the use of the proposed name, Razadyne.

**DMETS Comments:** Since the complete proprietary name assessments for Razadyne and Razadyne ER were not submitted for review, DMETS cannot comment of the conclusions reached by [ ] for these proprietary names.

III. **RECOMMENDATIONS:**

- A. DMETS has no objections to the use of the proprietary name Razadyne/Razadyne ER from a safety perspective. However, DMETS would like to recommend that the sponsor provide adequate education for healthcare providers of the availability of the extended-release product and the name change from Reminyl to Razadyne with launch of the product.
- B. DDMAC does not object to the name Razadyne from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

/s/

---

Kim Culley, RPh  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

/s/

Concur:

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Alina Mahmud, RPh, MS  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Appendix A. Prescription Studies for Razadyne

<b>Verbal</b>	<b>Inpatient</b>	<b>Outpatient</b>
Ravidine	Razadyne	Razadyne
Razodyne	Ragadyne	Razadyne
Rabidine	Razadyne	Razadyne
Razidyne	Ragadny	Razadyne
Ramidine	Razadyne	Razadyne
Razidine	Ragodyne	Rorzadyne
Renzyme	Razadyne	Rarzadyne
Ravidine	Razadyne	Razadyne
Ravadime	Razadyne	Razadyne
Ravadime	raznolyne	Razadyne
Remanide	Razadyne	Razadyne
	Razadyne	Ranzadyne
	Razadyne	Razadyne
	Razadyne	Rayadyne
	Ragadyne	
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/s/

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Kimberly Culley  
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DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
3/31/05 04:33:54 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
3/31/05 04:37:53 PM  
DRUG SAFETY OFFICE REVIEWER

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION</b>		<b>ODS POSTMARKETING SAFETY REVIEW</b>	
<b>FROM: Charlene Flowers, RPh Safety Evaluator, Division of Drug Risk Evaluation (HFD-430)</b>		<b>DATE: 2/2/2005</b> <b>ODS PID # D050074</b>	
<b>TO: Russell Katz, M.D. Director, Division of Neuropharmacologic Drug Products (DNBP), HFD-120</b>		<b>THROUGH: Mark Avigan, MD, CM Director, Division of Drug Risk Evaluation Office of Drug Safety (HFD-430)</b>	
<b>DRUG (Est)/APPROVAL: 2/01, 6/01, 12/04</b>	<b>NDA#s: 21-169, 21-224, 21-615</b>	<b>SPONSOR: Janssen</b>	
<b>DRUG NAME (Trade): galantamine (Reminyl)</b>		<b>THERAPEUTIC CLASSIFICATION: cholinesterase inhibitor for the treatment of Alzheimer's dementia</b>	
<p><b>Executive Summary:</b> A search of the AERS database was carried out to determine whether AERS reports are consistent with preliminary safety information from two placebo controlled Reminyl studies which showed higher mortality rates in drug-treated patients than in placebo-treated patients.<sup>1</sup> The causes of death were mainly cardiovascular or cerebrovascular in nature. Of the 1068 reports in the AERS database associated with Reminyl (galantamine), the most frequently reported preferred term (PT) was death (82). A review the 82 death reports revealed that the majority of cases (&gt;80%) were <u>solicited/stimulated</u> reports via the "Patient Assistance/Reminyl Experience" Program and contained little information including no mention of the cause of death. In the remaining reports of death (PT), most cases did not report a cause of death and 3 cases attributed the cause of death to disease progression.</p> <p>Reminyl (galantamine) is one of 4 cholinesterase inhibitors, currently on the US market, indicated for the treatment of dementia of the Alzheimer's type. Table 1 below displays the total number of AERS reports, number of deaths, number of serious outcomes, and the top 20 preferred terms (PTs) for each of the products. The majority of the top 20 PTs are labeled events. Although Reminyl shows death as the top PT, a preponderance of the reports (67 of 82) were solicited/stimulated. After removing these 67 non-spontaneous reports, the percentage of reports with fatal outcomes relative to the total number of reports is comparable for all 4 cholinesterase inhibitors. Table 2 further stratifies the death reports based on age groups. As expected, the majority of deaths were reported in patients in the age range of 71 to 90 years. It must be remembered that the counts shown below are raw numbers and may contain duplicates.</p>			
<p><b>Reason for Request/Review:</b>  DDRE was asked by the Office of Executive Programs to comment on risk identified by 2 placebo controlled Reminyl studies that show higher mortality rates in the drug-treated patients versus placebo-treated patients. In order to identify the most commonly reported adverse events associated with Reminyl (galantamine), we carried out several searches in the AERS database for all 4 cholinesterase inhibitors currently on the US market.</p>			
<b>Search Date: 2/1/2005</b>		<b>Search Type(s): X AERS Literature Other</b>	
<p><b>Search Criteria:</b>  Drug Names: <b>Reminyl/galantamine, Exelon/rivastigamine, Aricept/donepezil, Cognex/tacrine</b>  Adverse Event: <b>All</b></p>			

<sup>1</sup> [http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/reminyl\\_pa\\_e.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/reminyl_pa_e.html)

**Search Results: The following counts are raw numbers and may contain duplicates**

**Table 1:**

<b>Reminyl® (galantamine)</b> NDA 21-169, 21-224, 21-615		<b>Exelon® (rivastigamine)</b> NDA 20-823, 21-025		<b>Aricept® (donepezil)</b> NDA 20-690, 21-719, 21-720		<b>Cognex® (tacrine)</b> NDA 20-070	
FDA approval date(s)	2/01 6/01 12/04	FDA approval date(s)	4/00 4/00	FDA approval date(s)	11/96 10/04 10/04	FDA approval date(s)	9/93
<b>Total # AERS reports</b>	1068	<b>Total # AERS reports</b>	935	<b>Total # AERS reports</b>	3938	<b>Total # AERS reports</b>	4427
<b># Deaths<sup>2</sup></b>	247	<b># Deaths<sup>2</sup></b>	151	<b># Deaths<sup>2</sup></b>	419	<b># Deaths<sup>2</sup></b>	616
<b>Serious Outcomes<sup>3</sup></b>	796	<b>Serious Outcomes<sup>3</sup></b>	844	<b>Serious Outcomes<sup>3</sup></b>	2402	<b>Serious Outcomes<sup>3</sup></b>	1454
<b>Top 20 AERS Preferred Terms</b>	<b>Count (raw)</b>	<b>Top 20 AERS Preferred Terms</b>	<b>Count (raw)</b>	<b>Top 20 AERS Preferred Terms</b>	<b>Count (raw)</b>	<b>Top 20 AERS Preferred Terms</b>	<b>Count (raw)</b>
Death <sup>‡</sup>	82	Vomiting*	90	Diarrhea*	292	Vomiting*	500
Vomiting*	56	Nausea*	83	Confusional State*	282	Nausea*	404
Confusional State*	54	Confusional State*	76	Vomiting*	266	Alanine Aminotransferase Increased*	348
Fall*	51	Fall	55	Nausea*	248	Drug Ineffective	335
Dizziness*	49	Syncope*	51	Agitation*	217	Confusional State*	332
Nausea*	48	Dizziness*	49	Dizziness*	200	Hepatic Function Abnormal*	331
Cerebrovascular Accident	47	Convulsion*	45	Syncope*	187	Condition Aggravated	287
Bradycardia*	45	Dyspnea*	44	Bradycardia*	186	Agitation*	262
Agitation*	42	Asthenia*	42	Asthenia*	177	Anorexia*	247
Syncope*	40	Agitation*	40	Drug Interaction	173	Diarrhea*	244
Somnolence*	36	Bradycardia*	40	Condition Aggravated	164	Weight Decreased	236
Medication Error	35	Hallucination*	37	Convulsion*	161	Hallucination*	161
Condition Aggravated	34	Hyperhidrosis*	34	Insomnia*	161	Accident	149
Anorexia*	30	Anorexia*	32	Fall	143	Dizziness*	149
Myocardial Infarction	30	Drug Interaction	29	Anorexia*	137	Asthenia*	143
Pneumonia	30	Coma*	28	Sedation*	130	Abdominal Pain*	137
Tremor*	30	Diarrhea*	28	Tremor*	117	Hostility*	129
Diarrhea*	29	Hypertension*	28	Hallucination*	111	Sedation*	129
Drug Interaction	29	Disorientation*	27	Drug Ineffective	100	Dermatitis*	121
Convulsion*	28	Loss of Consciousness*	27	Headache*	92	Convulsion*	119

<sup>‡</sup> NOTE: Patient Assistance/Reminyl Experience Program stimulated 67 reports of death(PT)

\*labeled events

<sup>2</sup> See next table for death cases stratified by age groups

<sup>3</sup> A case may report more than one outcome. Serious outcomes include one or more of the following: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, or required intervention to prevent permanent impairment/damage

**Table 2: Death reports stratified by age groups**

Reminyl® (galantamine) NDA 21-169, 21-224, 21-615		Exelon® (rivastigamine) NDA 20-823, 21-025		Aricept® (donepezil) NDA 20-690, 21-719, 21-720		Cognex® (tacrine) NDA 20-070	
Age Group	Count	Age Group	Count	Age Group	Count	Age Group	Count
41 - 50 yrs	2	41 - 50 yrs	1	41 - 50 yrs	2	41 - 50 yrs	2
51 - 60 yrs	8	51 - 60 yrs	1	51 - 60 yrs	6	51 - 60 yrs	13
61 - 70 yrs	8	61 - 70 yrs	7	61 - 70 yrs	53	61 - 70 yrs	70
71 - 80 yrs	55	71 - 80 yrs	45	71 - 80 yrs	144	71 - 80 yrs	265
81 - 90 yrs	72	81 - 90 yrs	73	81 - 90 yrs	145	81 - 90 yrs	195
90 +	17	90 +	14	90 +	19	90 +	14
Null Age Values	85	Null Age Values	10	Null Age Values	50	Null Age Values	57
<b>Total</b>	<b>247</b>	<b>Total</b>	<b>151</b>	<b>Total</b>	<b>419</b>	<b>Total</b>	<b>616</b>

Reviewer's Signature / Date: *Charlene Flowers, RPh*  
2/2/05

Team Leader's Signature / Date: *Cindy Kortepeter, Pharm.D.*  
2/2/05

Division Director Signature / Date:

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Mark Avigan  
2/8/05 02:44:04 PM  
DRUG SAFETY OFFICE REVIEWER

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** January 24, 2005  
**Application:** NDA 21-615; Reminyl (galantamine hydrobromide) extended release capsules, immediate release tablets, and oral solution  
**Indication:** Mild to moderate dementia of Alzheimer's disease  
**Type of Meeting:** Transition plan for name change  
**Meeting Chair:** Russell Katz, M.D.  
**Meeting Recorder:** Melina Griffis, RPh.

### FDA Attendees:

Russell Katz, M.D., Division Director	Alice Hughes, M.D., Safety Reviewer
Ranjit Mani, M.D., Medical Officer	Denise Toyer, R.Ph., DMETS
Judy Racoosin, M.D., Safety Team Leader	Carol Holquist, R.Ph., DMETS
Courtney Calder, PharmD, Project Manager	Sally Yasuda, Ph.D., Biopharm.
Christine Garnett, PharmD, Pharm/Tox Reviewer	Melina Griffis, RPh, Project Manager

### Johnson & Johnson Attendees:

James Medley, PhD, US Reg. Liaison	Bert Bruce, Ortho-McNeil Neuropharm
Luc Truyen, MD, Ph.D., Acting Compd. Dev. TL	Suzanne Foy, Global Regulatory Affairs
Martin Gilligan, Pharm. Global Strategic Market.	Qin Ying Zhao, Clin. Pharm. & PK
Linda Carter, Global Reg Affairs, FDA Liaison Off.	Stephanie Ciarracca, Pharm. Source. Grp.
Bob Brasier	

**This meeting was held to discuss a plan to implement a change in the proprietary name for galantamine hydrobromide.**

**Below are key items discussed and agreements reached between the Division and sponsor.**

### New Product Name

1. Although the Division of Drug Marketing, Advertising, and Communications (DDMAC) had found the product name [ ] to be acceptable, DMETS has recommended that this name not be used since it has the potential for being confused with the product names of other marketed drugs; this Division therefore recommended against its use.
2. Notwithstanding the recommendation from DDMAC against the use of the product name [ ] DMETS is currently reviewing this name for the possibility that its use could result in errors, such as might occur during dispensing and prescribing. The negative recommendation from DDMAC does not preclude the possibility that, if the assessment by DMETS is favorable, the sponsor might be able to use the name [ ] instead of Reminyl®.
3. Two additional proprietary names very recently proposed by the sponsor [ ] are currently under review by both DMETS and DDMAC.

Transition Plan

1. The Division was concerned that over a specific period in the transition process, at least 3 differently labeled containers for galantamine formulations would be available and would create a potential for medication errors. The 3 different labels would be those for:
  - a. The extended-release formulation using the new proprietary name
  - b. The immediate-release formulation using the old and new proprietary names
  - c. The immediate-release formulation using the old proprietary name
2. After a lengthy discussion, it was decided that this concern could best be addressed by launching the extended-release formulation labeled with the new proprietary name and the dual-labeled immediate-release products (labeled both with the new proprietary name and a "formerly known as Reminyl" statement) at the same time.
3. The Division recommended that communications to physicians, pharmacists, and others during the transition process be more explicit and detailed than they are currently; for example, it should be made very clear that the new and old product names apply to the same drug, and the use of both the old and new formulations together warned against. There were additional discussions about the recipients and text of these communications. The Division also recommended that the sponsor explain why the change was being made.
4. The sponsor has proposed that patients already taking a twice daily dose of immediate-release galantamine tablets or galantamine oral solution, who wish to change to the extended-release formulation, begin taking once-daily extended-release capsules in the same total daily dose without titration. This proposal is acceptable to the Division.
5. Several communications that are part of the transition package state that extended-release galantamine has the same efficacy as the immediate-release formulation and that the former is better tolerated than the latter. The Division indicated that these statements may not be adequately supported by the results of Study GAL-INT-10.

Other Issues

Mortality in Studies of Galantamine for MCI

The sponsor summarized the status of their investigation of the mortality excess in galantamine-treated patients in MCI studies compared with placebo regarding the numbers of death cases following the retrieval of information about patients who dropped out.

Minutes Preparer: \_\_\_\_\_  
Melina Griffis R.Ph.

Chair Concurrence: \_\_\_\_\_  
Russell Katz, M.D.

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/s/

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Russell Katz  
2/18/05 08:17:59 AM

## MEMORANDUM

DATE: December 21, 2004

FROM: Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-615

SUBJECT: Recommendation for Action on NDA 21-615, Reminyl Extended Release Capsules for the treatment of mild to moderate Alzheimer's Disease

NDA 21-615, Reminyl Extended Release Capsules for the treatment of mild to moderate Alzheimer's Disease, was submitted by Johnson & Johnson Pharmaceutical Research, on 2/24/03. The application contained the results of a single controlled trial that compared the immediate release tablet (currently approved for the same indication), the extended release capsule, and placebo in patients with mild to moderate Alzheimer's Disease. In that study, the comparison between the extended release capsule and placebo did not reach statistical significance on the CIBIC (one of the two co-primary outcomes;  $p=.2$ ), although the drug-placebo comparison for the other co-primary outcome (ADAS-Cog) did reach significance. The results were the same for the approved tablet-placebo comparisons. The comparison between the extended release capsules and placebo on the only other global/functional measure assessed in the study, the ADCS-ADL, was nominally significant ( $p<.001$ ).

Because of the lack of significance of the ER-placebo comparison on the CIBIC, one of the two prospectively identified co-primary outcome measures, the division issued a Not Approvable letter on 12/23/03. The sponsor submitted a response to that letter, which was the subject of a second Not Approvable letter dated 7/27/04.

In response to the second NA letter, the sponsor submitted a Dispute Resolution Request to Dr. Robert Temple, Director, Office of Drug Evaluation I. In a memo dated 10/26/04, Dr. Temple concluded that substantial evidence of effectiveness had been provided.

In response to Dr. Temple's decision, the sponsor has submitted, on 10/27/04, additional information, including proposed labeling, CMC and dissolution data, and a proposal related to the product's proposed name.

Regarding this latter issue, we are aware of several reports of medication errors involving Reminyl and Amaryl, an oral hypoglycemic medication. Unfortunately, we have received reports of two deaths related to elderly patients having received Amaryl instead of Reminyl; presumably the deaths were related to

hypoglycemia. In discussions with the sponsor subsequent to this current submission, we have agreed that they will change the name of Reminyl products (see below).

The current package has been reviewed by Dr. Ranjit Mani, medical officer (review dated 12/14/04), Dr. Ronald Kavanagh, Office of Clinical Pharmacology and Biopharmaceutics (review dated 11/30/04 and a second, undated review), and Dr. Janusz Rzeszutarski, chemist (review dated 11/29/04). Dr. Mani continues to recommend that the application be considered Not Approvable.

The sponsor has presented numerous post-hoc analyses and arguments to support their view that the single study submitted demonstrates the effectiveness of the extended release capsules (e.g., statistically significant drug-placebo comparison on the ADCS-ADL; analyses adjusted for baseline differences; separate analyses of the US centers; a claim that the prospectively designated analysis of the CIBIC was inappropriate; analyses of a subset of patients with a particular range of scores on the MMSE at baseline, etc.). These analyses are described in detail by Dr. Mani, and I have commented on several of these in my memos of 12/23/03 and 7/27/04. In my view, the sponsor has offered no new analyses/arguments that are compelling, and I am not convinced by any of these arguments that the application should be approved. However, of course, I acknowledge that Dr. Temple has already reached a very different (and I must admit a not unreasonable) conclusion. Because of this, we have negotiated labeling with the sponsor, and have agreed with them on a final draft. Further, they have addressed all other issues, and the application can be approved.

One other important issue needs to be addressed further.

As described above, we are aware of several medication errors related to the similarity of the name Reminyl to Amaryl. We have been in frequent contact with the sponsor about ways to minimize these errors in the future, and the sponsor has instituted a multi-pronged education campaign to make prescribers and patients aware of the potential for this error. Upon learning of a second death related to this confusion, we have agreed with the sponsor that they must, and will, change the name of all Reminyl products. We have not, as of this time, agreed on a new name for this product line (as of this writing, the sponsor has decided to continue to market the other oral dosage forms [tablet and oral solution] simultaneously with the extended release capsule). Because we have not agreed on a new name, the extended release products will be approved without a trade name, and will not be marketed until we can agree with the sponsor on an acceptable new name. When we agree with the sponsor on a new name, the name of all Reminyl products will be changed. Also, because the current Reminyl product will remain on the market, as Reminyl, the extended-release capsules will be approved with separate labeling. The educational campaign will continue to be employed as long as it is deemed necessary.

We are forwarding the draft Approval letter (with attached agreed-upon draft labeling) for Dr. Temple's signature.

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/s/

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Russell Katz  
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MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 26, 2004

FROM: Director, Office of Drug Evaluation I. HFD-101

SUBJECT: NDA 21-615 – Reminyl (galantamine hydrobromide) ER Capsules

TO: File

I. Introduction

NDA 21-615 [Johnson and Johnson Pharmaceutical Research] is for an extended release (ER) formulation of galantamine hydrochloride (Reminyl) for the treatment of mild to moderate dementia of the Alzheimer's type (the same claim as the IR dosage form). Although the AUC and Cmin of the IR and ER met bioequivalence standards (80-125%), both were actually slightly, but significantly, lower for the ER, and for Cmax, the ER was both lower and outside the 80-125 bioequivalence limit (ratio 76%, 71-80). The Division, therefore, concluded that a clinical trial was needed to support the new dosage form. Study Gal-INT-10 (6 months) was carried out to support the application. At the Division's suggestion, it was a 3-arm trial (ER, IR, and placebo) with primary endpoints of ADAS-Cog/11 and CIBIC-plus (a global evaluation standard for Alzheimer's Disease studies), the same endpoints used in the 4 IR studies (3 of which, of 5-6 months duration, were the basis for approval; there was also a supportive 3 month IR study). An activities of daily living scale was used as a secondary endpoint.

Gal-INT-10 showed the desired effect on the ADAS-COG/11 but no clear effect on the CIBIC-plus. Table 1 shows the ER and IR results.

Table 1  
Results of Placebo-Controlled Trials

Study	Formulation	ADAS-Cog	Global (CIBIC-plus)	Function DAD or ADCS/ADL
Gal-INT-1	IR	<0.001	<0.08	NS
Gal-USA-1	IR	<0.001	<0.05	NS
Gal-INT-2	IR	<0.05	<0.05	<0.05
Gal-USA-10	IR	<0.001	<0.05	=0.002
Gal-INT-10	IR	<0.001	NS (p=0.144)	=0.018
	ER	<0.001	NS (p=0.216)	<0.001 (both ADCS ADL)

The standard for approval of drugs for dementia has been a demonstration of effectiveness (statistically significant superiority over placebo) on both a cognitive measure (the ADAS-Cog) and a global/functional measure, either the CIBIC-plus (or some variant) or an activities-of-daily-living scale (such as the ADCS-ADL, the scale used in Gal-INT-10). Although a global and ADL scale are equally acceptable, one of them is ordinarily chosen as the primary endpoint, and J&J chose the CIBIC-plus, perhaps because it was more consistently favorable than ADL in the IR studies (4/4 vs. 2/4 in the 4 IR trials). It would, of course, have been perfectly acceptable to use the CIBIC-plus and ADL scores as co-primary endpoints, testing each at

some p-value between 0.025 and 0.05 (0.025, a Bonferroni adjustment, seems extreme, as the two measures surely are somewhat correlated), but J&J did not do that. Ordinarily, we would not consider success on an undeclared endpoint a "success" if the designated primary endpoint failed even if the secondary endpoint was "reasonable," as it surely is here, but there have been exceptions, where other information was considered pertinent. [An illustration is our approval, supported by the Cardiovascular and Renal Drugs Advisory Committee, which included Tom Fleming, a fairly cautious biostatistician, of carvedilol for post-infarction/LV dysfunction improvement in survival based on the CAPRICORN Study. That study had, as its primary endpoints, both (1) total mortality plus all-cause hospitalization and (2) total mortality, but the critical p-value for total mortality was 0.01 (changed during the study from a single endpoint of total mortality with a critical alpha of 0.05) and the mortality/hospitalization endpoint was to be tested at 0.049. The results showed no real effect on the combined endpoint but a nominally significant effect on survival (p=0.03). After considerable discussion, this "failed" endpoint was accepted, based, among other things, on "prior" success of several beta-blockers on survival post-infarction and on a large body of evidence that carvedilol improves survival in patients with overt congestive heart failure. Plainly, a good deal of judgment went into this decision and the use of judgment was considered acceptable.]

In NA letters dated December 23, 2003 and July 27, 2004, the Division (Dr. Katz) rejected the Reminyl ER application as failing to provide substantial evidence of effectiveness because study Gal-INT-10 failed to show an effect on both of its primary endpoints (12/23) and because several post hoc analyses of the CIBIC-plus that were intended to correct various imbalances were not persuasive given the fundamental soundness of the original, protocol-specified analysis, and the many alternative analyses that might have been conducted.

## II. Appeal

The appeal argues that the "body of evidence" available provides substantial evidence of effectiveness, with a highly significant effect on a cognitive domain (ADAS-Cog), a global functional endpoint (ADCS-ADL), and even the CIBIC-plus, when reanalyzed to correct for several factors, which are explained in detail in various attachments. In particular, they argue that:

1. The trial had reduced assay sensitivity for CIBIC-plus compared to past trials, as indicated by the failure of the IR dosage to show the effect present in all previous 4 IR studies. This was caused, in part by excess weight in analyses that was given to non-U.S. sites, only 31% of the total, and to some imbalance of subjects with mild dementia who do not respond as well.
2. ADL is an accepted and legitimate endpoint.

## III. Conclusion and Reasons - Summary

I believe J and J has provided substantial evidence of the effectiveness of Reminyl ER. My reasons are as follows:

- A. For a well-evaluated drug, like galantamine, known in IR form to be effective in Alzheimer's Disease, an effect on the ADAS-Cog should be considered sufficient evidence that the ER form is effective.
- B. The results of the ADCS-ADL are strongly supportive of the ADAS-Cog results, even if this finding is not necessary and despite its non pre-specified nature.
- C. The failure of the ER to show an effect on the CIBIC-plus is greatly mitigated by the failure of the IR to have an effect on this endpoint in Gal-INT-10, when there is no doubt, from previous studies, that the IR (and thus galantamine) is a drug that affects both cognitive function and global measures.

- D. The alternative analyses of the CIBIC have, in several cases, and one in particular, the weighting of clinics, considerable merit even if they are post hoc.

#### IV. Conclusion and Reasons - Details

##### A. Sufficiency of ADAs-Cog

Approval of an alternative dosage form does not need the same level of clinical evidence as would be required for initial approval, particularly when it is bioequivalent (AUC) to the approved form. Indeed, in some cases, we have been prepared to rely on PK alone. In the present case, the equivalent AUC for a chronically used drug might itself have been sufficient (a main point, after all, of ER forms is to reduce the min/max swings) but, if not, what is needed is evidence that the altered PK leaves the pharmacologic effect of the drug intact including effect over the dosing interval. There is no short-term pharmacologic effect of galantamine to measure, but the most direct effect of an Alzheimer's drug's pharmacology is its effect on cognitive function. Although in evaluating a new agent, we ask, in addition, that there be evidence of an effect beyond cognition, i.e., that there is a meaningful effect on outcome (CIBIC-plus or ADL), this is a matter related to the therapeutic properties of the drug entity, not of a particular dosage form. I would argue that once it is established for galantamine, as the IR studies did, that the effect on cognition leads to global effect as well, a new dosage form that is essentially bioequivalent to the IR, need only show an effect on the ADAS-Cog.

##### B. The ADCS-ADL is supportive

Although we would, for initial approval, ordinarily not rely on an effect on a non-specified endpoint, we are not lacking in prior information here. We would expect such a global effect from a galantamine dosage form that had an effect on the ADAS-Cog. Moreover, ADL is not an unfamiliar endpoint, one chosen out of the blue, but one of the two standard global endpoints. Dividing the planned  $\alpha$  as 0.03 for each would have been acceptable and, as we know, the need to "win" on 2 endpoints is a challenge, considerably harder than showing an effect on a single endpoint. The very strong ADL finding should not be taken lightly. Note also that it was stronger for the ER than for the IR.

##### C. Failure of IR on CIBIC-plus is mitigating

Even if one were to speculate that it was the variation in PK (diminished Cmax) that somehow led to preserved effect on ADAS-Cog but loss of effect on CIBIC-Plus, the failure of the IR to show an effect on the CIBIC-plus undermines that speculation. This study could not detect an effect of either galantamine dosage form on the CIBIC-plus.

##### D. The standard analyses are very odd

I am not making an attempt to assess J&J's after-the-fact modifications of the CIBIC-plus, which are plausible enough but unequivocally retrospective, but I have long been dissatisfied with our obsession with by-clinic effects, weighting large and small clinics similarly, and doing things like grouping several small clinics for purposes of analysis. In the present case, the initial analysis weighted U.S. and non U.S. regions equally, even though the U.S. sites had 69% of the population. In my view, the proper unit for analysis is ordinarily the patient and I would think clinics would be weighted in accordance with their contribution to the patient sample. Although I am not trying to settle this issue, and based on A-C above, consider Reminyl ER approvable, this matter deserves further discussion.

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/s/

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Robert Temple  
10/26/04 04:02:23 PM  
MEDICAL OFFICER

## MEMORANDUM

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

TO: File, NDA 21-615

SUBJECT: Action Memo for NDA 21-615, for Reminyl (galantamine hydrobromide) Extended Release Capsules

NDA 21-615, for Reminyl (galantamine hydrobromide) Extended Release Capsules for once a day dosing, was submitted by Johnson and Johnson Pharmaceutical Research on 2/24/03. Reminyl, a cholinesterase inhibitor, is approved for twice a day dosing in an immediate release formulation. NDA 21-615 consisted of the results of a 26 week randomized, parallel group, controlled trial in which patients were randomized to Reminyl ER, IR, or placebo. The primary outcomes were the ADAS-Cog and the CIBIC-plus. Both Reminyl ER and IR were demonstrated to be statistically superior to placebo on the ADAS-Cog, but not on the CIBIC-Plus. For this reason, the division issued a Not Approvable letter on 12/23/04. In this letter, we informed the sponsor that they would need to conduct an additional controlled trial that demonstrated statistically significant superiority of Reminyl ER to placebo on a cognitive and a global measure in order for the drug to be approved. We met with the sponsor on 2/17/04 to discuss the basis for the Division's action, as well as approaches to establishing the effectiveness of the product. At that meeting, we informed the sponsor that if they could provide a compelling argument for disregarding the results on the CIBIC-Plus and justify relying on the results of the ADCS-ADL instead (the only other outcome measured in the study that could be considered an acceptable "global measure", it was nominally statistically significant, but was one of many secondary measures assessed in the study), we would be willing to consider such an approach.

The sponsor has submitted a complete response to the 12/23/04 Not Approvable letter on 5/27/04. The response consists of multiple re-analyses of the CIBIC-Plus that the sponsor contends are more appropriate than the one performed on this measure in the original submission. This complete response has been reviewed by Dr. Ranjit Mani, medical officer (review dated 7/26/04) and Dr. Kun He, statistician (review dated 7/12/04). Neither reviewer finds the sponsor's analyses compelling.

Briefly, the protocol specified analysis of the CIBIC-Plus was a CMH using modified ridit scores and stratified by region (US vs non-US). This analysis (ITT, LOCF) yielded a between-treatment p-value of 0.22 for the ER-placebo contrast. In the re-submission, the sponsor presented the results of numerous, post-hoc, analyses, the results of which yield nominally significant between-treatment contrasts. For example, analyses stratified by baseline MMSE scores and

country, by baseline ADAS-Cog and country, by prior cholinomimetic use and country, and analyses of the US data only (69% of the total patient enrollment) yielded nominally significant between-treatment differences (p-values typically between 0.02 and 0.03).

Of particular interest was a CMH analysis stratified by study site. The sponsor contends that stratifying by study site is more appropriate than the stratification used in the protocol-specified analysis (by country) because the randomization was stratified within site, and because the stratification by country weights the contribution of the two regions equally, while the US contributed 69% of the patients. In this new analysis, centers with fewer than 3 patients per treatment group were pooled, creating a center with 88 ER patients and 89 placebo patients (the next largest center had 21 ER patients and 22 placebo patients; typical centers had about 4-10 patients/treatment group). The p-value for this analysis was  $p=0.03$  (the p-value for the pooled "center" was 0.029, with no other center nominally significant [see Dr. He's review, page 7]).

## COMMENTS

The sponsor has presented numerous re-analyses of the CIBIC-Plus, one of the two co-primary outcomes in the controlled trial. These analyses are clearly post-hoc analyses, and, although perhaps of interest from an exploratory point of view, cannot be considered to provide definitive results. As I explained in my 12/23/03 memo, we would typically rely on the results of the protocol-specified analyses (in my memo, I discussed the issue as it pertained to relying on the protocol specified **outcome**, but the point with regard to multiple **analyses** of the original outcome measure is the same), unless there is reason to believe that the protocol-specified analyses were inappropriate. The sponsor has not provided any compelling argument that the original protocol-specified analysis of the CIBIC-Plus was flawed in any fundamental way. Perhaps the argument that the analysis should have been stratified by study site, and not country, given that the randomization was stratified within study site, is most attractive. However, obviously the sponsor was aware that the randomization was stratified within study site, yet the protocol still called for a stratification by country, which is, as Dr. He points out, the most typical type of stratification used for international studies. Further, the pooling plan was clearly not pre-specified, and it created an extremely large single "center", much larger than any other single center, and the overall nominally significant p-value appears to have been driven by this retrospectively created center. The creation of this very large single "center" seems to subvert the purpose of stratification by center, which is to evaluate the effect of the various centers. Further, it appears that this center was created by pooling both US and non-US small centers, a maneuver that in itself is problematic.

In summary, the sponsor has presented no compelling rationale for supplanting the protocol specified, standard, CMH analysis with any of their additional post

hoc re-analyses. Further, even if we had been convinced that the original analysis was inappropriate, the sponsor has not adequately justified the appropriateness of the numerous specific alternative analyses they performed, especially given the almost infinite alternative analyses that they could have performed. Finally, the specific analyses they have performed may themselves be problematic. For these reasons, I agree with Drs. Mani and He that the study must still be considered "negative", and I will issue the attached Not Approvable letter.

A handwritten signature in black ink, appearing to be the initials 'RS' or a similar monogram, enclosed within a slanted rectangular box.

Russell Katz, M.D.

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/s/

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Russell Katz  
7/27/04 10:18:06 AM  
MEDICAL OFFICER

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** February 17, 2004  
**Application:** NDA 21-615; Reminyl® ER  
**Indication:** Alzheimer's Disease  
**Type of Meeting:** End of Review Conference  
**Meeting Recorder:** Melina Griffis, R.Ph.

### FDA Attendees:

Russell Katz, M.D., Director	Ranjit Mani, M.D., Team Leader
Kun Jin, Ph.D., Biometrics Team Leader	Ray Baweja, Ph.D., Biopharm Team leader
Ron Kavanagh, Ph.D., Biopharm	Melina Griffis, R.Ph, Regulatory

### Janssen Attendees:

Joan Amatniek, M.D.	Michael Gold, M.D.
Suzanne Foy, R.Ph., Regulatory,	James Medley, Ph.D.
Luc Truyen, M.D., Ph.D.	Bert Bruce
Jeffrey Nye, M.D., Ph.D.	Qin Ying Zhao, Ph.D.
Daniel Wang, Ph.D.	Patricia DeSantis
Gordon Pledger, Ph.D.	Bob Brashear
Scott Reines, M.D., Ph.D.	Jack Singer, M.D.

### Discussion Points and Decisions (agreements) reached:

The meeting was requested by the sponsor to discuss the Division's December 23, 2003 Not Approvable letter for the controlled-release formulation of Reminyl®. The sponsor's and Division's viewpoints about the results of Study GAL-INT-10, and the next steps that the sponsor might take in obtaining approval of Reminyl® ER for the treatment of mild to moderate dementia of the Alzheimer's type, were discussed. The discussion included an outline of the sponsor's views as to why there was no evidence for the efficacy of either the extended-release or immediate-release formulations of Reminyl® on the CIBIC-Plus analysis in that study.

Based on that discussion, the following were the key agreements reached at the meeting

- The sponsor was advised to submit a detailed argument that addresses, on clinical and statistical grounds, why the results of the ADCS-ADL analysis for Study GAL-INT-10 should be considered in lieu of those for the CIBIC-Plus, in attempting to establish that that study is "positive".
- The sponsor proposed that another means of establishing the efficacy of the extended-release formulation of Reminyl® might be the demonstration of a correlation between exposure (based on AUC) and clinical effect, in a small study using the immediate-release formulation of Reminyl® alone, given the similarity in AUC between the 2 formulations of Reminyl®. The Division will comment more fully on such a proposal

once more details are submitted. Such a proposal should clearly describe how a link between clinical effectiveness and pharmacokinetic exposure will be established.

- The sponsor proposed that a further efficacy study of the extended-release formulation of Reminyl® use the ADAS-Cog and ADCS-ADL as primary efficacy measures and be of 3 months duration. This proposal will in all likelihood be acceptable to the Division, although 3 months is the minimum duration for an efficacy study in Alzheimer's Disease.
- A submission comprising one or more of the above would be considered a response to the Division's Not-Approvable action letter.

The sponsor asked if the nomenclature to be used for the proposed new formulation in labeling – Reminyl® ER (galantamine hydrobromide) Extended Release Capsules had been agreed to by the Division of Medication Errors and Technical Support (DMETS). The Division stated that the final opinion of DMETS was pending, however, preliminarily it appeared to be acceptable.

/s/

Minutes Preparer: \_\_\_\_\_  
Melina Griffis, R.Ph.

/s/

Chair Concurrence: \_\_\_\_\_  
(or designated signatory) Russell Katz, M.D.

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Russell Katz  
2/25/04 07:46:30 AM

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-615

10/26/04

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: James H. Medley, Ph.D.  
1125 Trenton-Harbourton Road  
P.O. Box 200  
Titusville, NJ 08560-0200

Dear Dr. Medley:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reminyl® (galantamine hydrobromide) Extended Release Capsules.

Your September 24, 2004, request for formal dispute resolution, received on September 27, 2004, concerns the Division of Neuropharmacological Drug Products' (DNDP) findings that the data submitted to NDA 21-615 were not adequate to support approval of Reminyl ER. Specifically, in the letter dated December 23, 2003, DNDP determined that you had not provided substantial evidence of effectiveness, based on the failure of the clinical efficacy study GAL-INT-10 to demonstrate an effect on both the ADAS-cog and the CIBIC-plus. Following your complete response of May 27, 2004, DNDP determined that you had not provided convincing rationale for considering the protocol-specified CIBIC-plus analysis inappropriate and therefore concluded that your post hoc re-analyses of the CIBIC-plus were inappropriate. This was communicated in the July 27, 2004 Not Approvable letter. Your appeal asserts that the body of evidence you have submitted to the division provides substantial evidence of effectiveness of Reminyl ER to support approval and requests that the Office of Drug Evaluation I resolve this dispute.

We have reviewed your appeal and conclude that you have provided substantial evidence of the effectiveness of Reminyl ER. Before the Reminyl ER application can be approved, however, you need to submit a complete response to the July 27, 2004 Not Approvable letter. Your complete response should reference this decision to address the deficiencies cited in the Not Approvable letter and include proposed labeling for review.

NDA 21-615

Page 2

If you have any questions, please call Ms. Kim Colangelo, Formal Dispute Resolution Project Manager, at (301) 443-5374.

Sincerely,

*[See attached electronic signature page]*

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

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/s/

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Robert Temple  
10/26/04 03:57:13 PM

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** February 17, 2004  
**Application:** NDA 21-615; Reminyl® ER  
**Indication:** Alzheimer's Disease  
**Type of Meeting:** End of Review Conference  
**Meeting Recorder:** Melina Griffis, R.Ph.

### FDA Attendees:

Russell Katz, M.D., Director	Ranjit Mani, M.D., Team Leader
Kun Jin, Ph.D., Biometrics Team Leader	Ray Baweja, Ph.D., Biopharm Team leader
Ron Kavanagh, Ph.D., Biopharm	Melina Griffis, R.Ph, Regulatory

### Janssen Attendees:

Joan Amatniek, M.D.	Michael Gold, M.D.
Suzanne Foy, R.Ph., Regulatory,	James Medley, Ph.D.
Luc Truyen, M.D., Ph.D.	Bert Bruce
Jeffrey Nye, M.D., Ph.D.	Qin Ying Zhao, Ph.D.
Daniel Wang, Ph.D.	Patricia DeSantis
Gordon Pledger, Ph.D.	Bob Brashear
Scott Reines, M.D., Ph.D.	Jack Singer, M.D.

### Discussion Points and Decisions (agreements) reached:

The meeting was requested by the sponsor to discuss the Division's December 23, 2003 Not Approvable letter for the controlled-release formulation of Reminyl®. The sponsor's and Division's viewpoints about the results of Study GAL-INT-10, and the next steps that the sponsor might take in obtaining approval of Reminyl® ER for the treatment of mild to moderate dementia of the Alzheimer's type, were discussed. The discussion included an outline of the sponsor's views as to why there was no evidence for the efficacy of either the extended-release or immediate-release formulations of Reminyl® on the CIBIC-Plus analysis in that study.

Based on that discussion, the following were the key agreements reached at the meeting

- The sponsor was advised to submit a detailed argument that addresses, on clinical and statistical grounds, why the results of the ADCS-ADL analysis for Study GAL-INT-10 should be considered in lieu of those for the CIBIC-Plus, in attempting to establish that that study is "positive".
- The sponsor proposed that another means of establishing the efficacy of the extended-release formulation of Reminyl® might be the demonstration of a correlation between exposure (based on AUC) and clinical effect, in a small study using the immediate-release formulation of Reminyl® alone, given the similarity in AUC between the 2 formulations of Reminyl®. The Division will comment more fully on such a proposal



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Russell Katz  
2/25/04 07:46:30 AM

**Griffis, Melina**

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**From:** Griffis, Melina  
**Sent:** Friday, January 09, 2004 10:12 AM  
**To:** 'Jim Medley (JMedley@PRDUS.JNJ.com)'  
**Subject:** NDA 21-615/Reminyl ER  
**Contacts:** Jim Medley

Hi Jim,

This email is to confirm that an End of Review conference has been scheduled on February 17, 2004 between 11:00-12:15 to discuss NDA 21-615. The location is 1451 Rockville Pike, 4th floor conference room.

Thanks  
Melina

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/s/

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Melina Griffis  
1/9/04 10:31:28 AM

**MEMORANDUM**

DATE: December 23, 2003

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

TO: File, NDA 21-615

SUBJECT: Action Memo for NDA 21-615, for the use of Reminyl (galantamine hydrobromide) Extended Release Capsules in patients with mild to moderate Alzheimer's Disease

NDA 21-615, for the use of Reminyl (galantamine hydrobromide) Extended Release Capsules in patients with mild to moderate Alzheimer's Disease, was submitted by Johnson & Johnson Pharmaceutical Research on 2/24/03. An immediate release formulation of Reminyl, approved for BID dosing, is currently marketed for the same indication. The current application contains the results of a single adequate and well-controlled clinical study (GAL-INT-10), a long-term open label uncontrolled extension to this study (GAL-INT-21), and 5 clinical pharmacology studies, as well as required CMC data. The extended release formulation is intended to be taken once a day.

The application has been reviewed by Dr. Ranjit Mani, medical officer (review dated 12/22/03), Dr. Kun He, statistician (review dated 11/26/03), Dr. Ronald Kavanagh, Office of Clinical Pharmacology and Biopharmaceutics (review dated 10/8/03), Dr. Janusz Rzeszotarski, chemist (review dated 12/18/03), and Dr. Martha Heimann, acting chemistry team leader (memo dated 12/19/03). Dr. Mani recommends that the application not be approved, and Dr. He concludes that the sponsor has not submitted evidence that Reminyl ER is effective. I will briefly review the relevant data, and offer the rationale for the Division's action.

As noted above, the application contains the report of a single adequate and well-controlled trial, in which patients with mild to moderate dementia of the Alzheimer's type were randomized to receive either Reminyl ER 16-24 mg once a day, Reminyl IR 8-12 mg twice a day, or placebo. The double-blind period was 26 weeks, and the primary outcome measures were the ADAS-Cog and the CIBIC-Plus.

The results of the analyses of these primary measures for the intent-to-treat population (ITT) on the last observation carried forward (LOCF) are presented below:

### ADAS-Cog

	<b>N</b>	<b>Change from Baseline</b>	<b>P-value vs Placebo</b>
Reminyl ER	291	-1.3	<0.001
Reminyl IR	296	-1.6	<0.001
Placebo	296	1.2	

<b>CIBIC-Plus</b>	<b>Reminyl ER (N=296)</b>	<b>Reminyl IR (N=302)</b>	<b>Placebo (N=301)</b>
Marked Imp	1%	1%	1%
Mod Imp	5%	6%	5%
Mild Imp	17%	15%	16%
No Change	39%	42%	37%
Mild Worse	27%	26%	27%
Mod Worse	10%	10%	14%
Marked Worse	2%	1%	2%
P-value vs Pbo	0.22	0.14	

The results of another potentially relevant outcome, the ADCS-ADL, are given below:

### ADCS-ADL

	<b>N</b>	<b>Change from Baseline</b>	<b>P-value vs Placebo</b>
Reminyl ER	296	0.0	<0.001
Reminyl IR	301	-1.0	0.018
Placebo	296	-2.7	

### COMMENTS

The sponsor has submitted a single randomized controlled trial designed to establish the effectiveness of an extended release formulation of Reminyl, a cholinesterase inhibitor known to be effective when given in an immediate release formulation. In cases such as this (a proposed new formulation of an approved compound), a single controlled trial of the new formulation is typically required, because we typically have no information about the relationship between plasma levels and effectiveness. Because this information is typically lacking (and is also specifically unavailable for Reminyl), it is possible that the differences seen in the kinetics between the two formulations might result in

differences in effectiveness; for this reason, a controlled trial with the new formulation is ordinarily required, as in this case.

Unfortunately, the single trial the sponsor conducted failed to meet its protocol-specified endpoint: statistically significant drug-placebo differences on both the ADAS-Cog and CIBIC-Plus, the two standard outcomes in trials of these agents. Specifically, while there was a clear statistically significant difference between drug and placebo on the ADAS-Cog ( $p < 0.001$ ), the p-value for the drug-placebo contrast on the CIBIC-Plus was 0.22 (ITT, LOCF analysis). Interestingly, the sponsor performed one additional measure of "global" functioning in this study; the ADCS-ADL, a measure we have accepted as a valid co-primary outcome measure in other similar studies (that is, instead of the more commonly used CIBIC-Plus). The p-value for the between-treatment contrast on this outcome was  $< 0.001$ . In this trial, the pattern of responses for Reminyl IR, the approved product, was similar to that seen for Reminyl ER; that is strongly significant between-treatment contrasts on the ADAS-Cog and ADCS-ADL, but a lack of significance ( $p = 0.14$ ) on the CIBIC-Plus.

It appears that, for all intents and purposes, Reminyl ER and IR performed similarly in this study; it could be argued, therefore, that we should conclude that Reminyl ER is effective. However, this conclusion does not follow logically from the data. It is true that Reminyl IR is effective (that is, it has been shown to separate statistically from placebo on the CIBIC-Plus on at least two prior occasions), but the fact that neither ER nor IR was shown to be significant on the CIBIC-Plus cannot imply that this should be ignorable for the ER. That is, despite the fact that IR has been shown to separate from placebo in the past on the CIBIC-Plus, this does not imply that the previous findings seen with IR on this outcome must apply to the ER, even though they responded similarly in this trial. Indeed, because we do not have previous experience with the ER, we cannot know that it will, ultimately, separate from placebo on this outcome; indeed, we require clinical trials with new formulations precisely because we do not know what the responses to them will be.

An argument can be made that the finding for Reminyl ER is so robust on the ADAS-Cog ( $p < 0.001$ ) that the lack of significance on the CIBIC-Plus should be ignorable. In my view, the finding on the ADAS-Cog, though yielding a very small p-value, does not, from a clinical point of view, ensure that the finding is, a priori, clinically important. Again, a statistically significant difference on the global measure is specifically required in order to "ensure" that the difference seen on the ADAS-Cog, regardless of the size of the p-value, is clinically important. Seen in this context, the lack of significance on the CIBIC-Plus raises concerns that the finding on the ADAS-Cog, is, in fact, of questionable clinical importance.

A more attractive argument, perhaps, in favor of approving the ER formulation is that the sponsor performed only one other measure of "global" functioning, the ADCS-ADL, a measure we have decided is an acceptable co-primary measure,

and that the between-treatment contrast on this measure yields a very small p-value ( $p < 0.001$ ). If we considered these 2 global measures (CIBIC-Plus, ADCS-ADL) as equally acceptable measures, and adjusted the alpha level accordingly (so that a p-value of 0.025 would be considered "significant"), then, clearly, the finding on the ADCS-ADL would be considered significant, and therefore should be accepted as the measure of global functioning necessary.

Unfortunately, by the usual rules of clinical trial analysis and interpretation, once the lack of significance on the primary outcome has been determined (in this case, the CIBIC-Plus), it is inappropriate to examine other, secondary measures, because this will inflate the overall experiment-wise Type I error; this is true even if the p-value for the between-treatment contrast on the secondary outcome is very small, as is the case here. It is true that in some past cases, we have "ignored" the results on the primary outcome and relied on the analysis of a particular secondary outcome on which to base a regulatory decision. In those cases, however, we had determined that the primary outcome, despite having been chosen prospectively, was considered inappropriate (for one reason or another), and therefore there was a rationale for considering a more clinically meaningful secondary outcome as primary. Clearly, in this case, the CIBIC-Plus is not an inappropriate co-primary outcome measure, and we cannot, therefore, ignore the results of the analysis of this measure.

For the reasons stated above, then, I will issue the attached Not Approvable letter.

A handwritten signature in black ink, appearing to be the initials 'RS' or a similar stylized name, enclosed within a slanted rectangular box.

Russell Katz, M.D.

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/s/

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Russell Katz  
12/23/03 10:21:55 AM  
MEDICAL OFFICER

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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** December 19, 2003

**TO:** NDA 21-615

**FROM:** Martha R. Heimann, Ph.D.

**SUBJECT:** **Overall Compliance and CMC Recommendations:**  
NDA 21-615, Reminyl (galantamine hydrobromide) Extended  
Release Capsules

The CDER Office of Compliance has issued an overall Acceptable recommendation for NDA 21-615. A copy of the establishment evaluation report is attached. Based on this, and Dr. Janusz Rzeszotarski's review dated December 18, 2003, the Office of New Drug Chemistry recommends approval of this application.

**Appears This Way  
On Original**

**Mille, Merrill J**

**From:** Mille, Merrill J  
**Sent:** Thursday, December 04, 2003 11:16 AM  
**To:** 'Medley, Jim [PRDUS]'  
**Subject:** RE: N21-615/Biopharm review

Jim,

Per your voice-mail request of 03-DEC-2003, here are our comments on the biopharm review for NDA 21-615/Reminyl.

The Biopharm review is complete.

1. OCPB finds the application acceptable.
2. OCPB has no general comments for the sponsor.
3. OCPB is recommending submission of additional dissolution data (not required for an approval action).

I do not have any other completed reviews to provide to you at this time.

Merril J. Mille, R.Ph.  
Consumer Safety Officer  
Phone: (301) 594-5528  
Fax: (301) 594-2859  
E-Mail: MilleM@cder.fda.gov

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/s/

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Merril Mille  
12/8/03 10:59:21 AM  
CSO

## Ware, Jacqueline H

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**From:** Levin, Randy (CDER)  
**Sent:** Friday, February 07, 2003 11:18 AM  
**To:** 'Medley, Jim [PRDUS]'; Claringbold, Ryan [PRDUS]  
**Cc:** Ware, Jacqueline H; Edmunds Jr, Kenneth  
**Subject:** RE: Size of Study Reports

The ICH guidance calls for a "List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study." This should not take up 60 MB.

-----Original Message-----

**From:** Medley, Jim [PRDUS] [mailto:JMedley@PRDUS.JNJ.COM]  
**Sent:** Friday, February 07, 2003 10:43 AM  
**To:** 'Levin, Randy (CDER)'; Claringbold, Ryan [PRDUS]  
**Cc:** Ware, Jacqueline H; Medley, Jim [PRDUS]; Edmunds Jr, Kenneth  
**Subject:** RE: Size of Study Reports

Dear Dr. Levin,

I apologize if for any miscommunication but let me try to clarify. We are following the ICH guidance on Clinical Study Reports and the CVs are provided in accordance with the ICH E3 Guidance on the Structure and Content of Clinical Study Reports. Since we are submitting this registration file simultaneously in several regions in the CTD format, we are providing all necessary appendices for all regions in a single common document.

I hope this explanation clarifies the situation. If not, please let me know and I will respond in more detail next week.

Thank you,  
Jim Medley,

Best Regards,  
James H. Medley, Ph.D.  
Associate Director, Global Regulatory Affairs  
Registratiezaken Wereldwijde  
Johnson & Johnson Pharmaceutical Research and Development, LLC.  
Ph. (609) 730-3049  
Fax (609)-730-2330  
Jmedley@prdus.jnj.com

-----Original Message-----

**From:** Levin, Randy (CDER) [mailto:LEVINR@cdcr.fda.gov]  
**Sent:** Thursday, February 06, 2003 9:31 PM  
**To:** 'Claringbold, Ryan [PRDUS]'  
**Cc:** Ware, Jacqueline H; Medley, Jim [PRDUS]; Edmunds Jr, Kenneth  
**Subject:** RE: Size of Study Reports

My first questions is why are you providing the CVs?

-----Original Message-----

From: Claringbold, Ryan [PRDUS] [mailto:RCLARIN1@PRDUS.JNJ.COM]  
Sent: Thursday, February 06, 2003 4:59 PM  
To: 'levinr@cdcr.fda.gov'  
Cc: 'warej@cdcr.fda.gov'; Medley, Jim [PRDUS]  
Subject: Size of Study Reports

Dear Dr. Levin,

We would like to request a waiver of the recommendation in the Guidance for Industry on Providing Regulatory Submissions in Electronic Format--NDAs for a 50 MB maximum file size for the clinical study reports for our NDA 21-615 for REMINYL (galantamine hydrobromide) Extended Release Capsules. The file size for our clinical study report for the single safety and efficacy trial for this pending NDA is approximately 73 MB. We realize that this file size will be more difficult for the reviewing division but we are unable to provide a logical breakpoint for dividing this into multiple files smaller than 50 MB as suggested in the guidance document. This study report contains a lengthy appendix of Investigator CV's which is approximately 60 MB in size. Since we receive these CVs in paper copy only, we must provide them in the electronic submission as scanned files. Although it might be possible to subdivide this appendix into smaller files, we feel that the subdivision would be arbitrary and confusing. Therefore we propose to submit the complete study report as a single file of 73 MB.

If this proposal is not acceptable, you may contact me directly or forward your concerns to Jim Medley, 609-730-3049, jmedley@prdus.jnj.com.

cc: Jackie Ware, Project Manager

Ryan Claringbold  
GRO, Global Dossier Leader  
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Phone: (908) 704-5976  
Cell: (908) 303-0996  
Fax: (908) 707-3376  
email: rclarin1@prdus.jnj.com  
Our Service Theme:           CREATING EXCELLENCE WITH WORLD CLASS ATTITUDES  
Our Service Standards:    QUALITY \* COURTESY \* TEAMWORK \*  
EFFICIENCY

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/s/

-----  
Jackie Ware  
2/10/03 07:17:15 PM  
CSO

**Mille, Merrill J**

**From:** Mille, Merrill J  
**Sent:** Tuesday, November 04, 2003 1:41 PM  
**To:** 'Medley, Jim [PRDUS]'  
**Subject:** RE: N21-615

Jim,

We need the SAS codes for deriving the results of Table 14 to Table 18 in Study Report of GAL-INT-10? You may send it to me via e-mail and follow up with a hard copy submission to the NDA or submit the material electronically to the electronic document room.

Merril

Merril J. Mille, R.Ph.  
Consumer Safety Officer  
Phone: (301) 594-5528  
Fax: (301) 594-2859  
E-Mail: MilleM@cder.fda.gov

11/4/2003

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/s/

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Merril Mille  
11/4/03 01:42:34 PM  
CSO

Mille, Merrill J

---

**From:** Mille, Merrill J  
**Sent:** Monday, October 27, 2003 10:13 AM  
**To:** 'Medley, Jim [PRDUS]'  
**Subject:** RE: N21-615

Jim,

Thank you for the speedy reply to our last week's query. Please respond to the following:

1. We note from your Attachment 5 to 3.2.P.5.4 (Batch Analyses) part, that the specifications for API Galantamine HBr differ from the specifications for the approved NDAs 20-169 and 21-224. Explain.
2. Submit an amendment to NDA 21-615 providing the specifications for the API Galantamine HBr.

Merril

Merril J. Mille, R.Ph.  
Consumer Safety Officer  
Phone: (301) 594-5528  
Fax: (301) 594-2859  
E-Mail: MilleM@cder.fda.gov

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/s/

-----  
Merril Mille  
10/27/03 11:36:09 AM  
CSO

Mille, Merrill J

---

**From:** Mille, Merrill J  
**Sent:** Thursday, October 23, 2003 2:06 PM  
**To:** 'Medley, Jim [PRDUS]'  
**Subject:** RE:N21-615

Dr. Medley,

In regard to NDA 21-615/Reminyl Extended Release, submit the Certificates of Analysis for the drug substance used in manufacturing of the — Registration Batches listed in the NDA.

Merril

Merril J. Mille, R.Ph.  
Consumer Safety Officer  
Phone: (301) 594-5528  
Fax: (301) 594-2859  
E-Mail: MilleM@cder.fda.gov

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/s/

-----  
Merril Mille  
10/23/03 02:06:58 PM  
CSO



Stephen Aronson, M.D.  
Mood & Memory Clinic of Michigan  
26105 Orchard Lake Rd, Suite #101  
Farmington Hills, Michigan 48334

SEP - 8 2003

Dear Dr. Aronson:

Between June 30 and July 21, 2003, Ms. Alanna Mussawwir-Bias, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # GAL-INT-10 entitled "Placebo controlled evaluation of galantamine in treatment of Alzheimer's Disease: Safety and efficacy of a controlled release formulation") of the investigational drug galantamine (Reminyl Extended Release Capsules), performed for Johnson & Johnson Pharmaceutical Research & Development, L.L.C. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Mussawwir-Bias presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your letter dated July 29, 2003 and wish to emphasize the following:

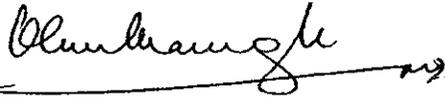
1. You did not maintain adequate and accurate records [21 CFR 312.62(b)].

Two subjects (A32199 and A32028) had to stop the study medication because they experienced adverse events (AE); namely, subject A32199 was noted to have worsened respiratory status, diarrhea, weakness and confusion; and subject A32028 experienced episodic vomiting. However, these adverse events are not recorded in their case report forms as the reason for early termination from the study.

Page 2 – Stephen Aronson, M.D.

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

Sincerely yours,

A handwritten signature in black ink, appearing to read "Khin Maung U", with a horizontal line extending to the right from the end of the signature.

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

FEI:

Field Classification: VAI

Headquarters Classification:

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

cc:

HFA-224  
HFD-120 Doc.Rm. NDA 21-615  
HFD-120 Review Div.Dir. Katz  
HFD-120 MO Mani  
HFD-120 PM Griffis  
HFD-46 c/r/s GCP File #10970  
HFD-46 MO Khin  
HFD-46 CSO Friend  
HFR-CE750 DIB Dempster  
HFR-CE750 BIMO Bellamy  
HFR-CE750 Field Investigator Mussawwir-Bias  
GCF-1 Seth Ray

r/d:NK: 8/27/03

reviewed:KMU:8/03

f/t:sg:8/28/03

O:\NK\NK\_Letters\Aronson.vai.doc

**Reviewer Note to Rev. Div. M.O.**

- For this study, 26 subjects were enrolled at the site.
- An audit of 9 subjects' records was conducted.
- Inspectional findings: Documentation indicates that two subjects (A32199 and A32028) experienced adverse events (AE), which led to the stop of the study medication. Specifically, the caregiver of subject A32199 reported that the subject had weakness, worsening of respiratory status, diarrhea, and confusion; and subject A32028 experienced episodic vomiting. However, their case report forms did not include AE as the reason for early termination from the study.
- In the EIR, it was noted that three subjects (A32200, A31885, A31274) who had medical conditions were included in the study, based on clinical judgement of the significance of their conditions by the PI. During the study, these subjects developed serious adverse events, which were reported to the sponsor.
- Overall, data appear acceptable.

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/s/

-----  
Khin U  
9/10/03 09:44:10 AM



Food and Drug Administration  
Rockville MD 20857

AUG 25 2003

Jerome Goldstein, M.D.  
The San Francisco Clinical Research Center  
909 Hyde St, Suite #322  
San Francisco, California 94109

Dear Dr. Goldstein:

Between June 27 and July 1, 2003, Mr. Jeffrey W. Shrifter, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # GAL-INT-10 entitled "Placebo controlled evaluation of galantamine in treatment of Alzheimer's Disease: Safety and efficacy of a controlled release formulation") of the investigational drug galantamine (Reminyl Extended Release Capsules), performed for Johnson & Johnson Pharmaceutical Research & Development, L.L.C. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

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

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

Sincerely yours,

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

Page 2 -- Jerome Goldstein, M.D.

FEI:

Field Classification: NAI

Headquarters Classification:

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

cc:

HFA-224

HFD-120 Doc.Rm. NDA 21-615

HFD-120 Review Div.Dir. Katz

HFD-120 MO Mani

HFD-120 PM Griffis

HFD-46 c/r/s GCP File #10462

HFD-46 MO Khin

HFD-46 CSO Friend

HFR-PA150 DIB Moss

HFR-PA150 BIMO Almogela

HFR-PA150 Field Investigator Swifter

GCF-1 Seth Ray

r/d:NK: 8/15/03

reviewed:KMU:8/03

f/t:sg:8/18/03

O:\NK\NK\_Letters\Goldstein.nai.doc

**Reviewer Note to Rev. Div. M.O.**

- For this study, 39 subjects were screened and 29 subjects completed the study. One subject transferred to this site from Subjects A31666 and A31667 were listed as screen failures due to cardiac abnormalities. Three subjects withdrew consent. Subject A32078 was not randomized due to alcohol abuse. Subject A32108 withdrew from the study at visit 3 due to adverse events of nausea and dizziness and subject A32307 discontinued after visit 4 due to SAE and spouse illness.
- An audit of all subjects' records was conducted. According to the EIR, the source documents and CRFs of subjects from this site agreed with data listing submitted by the sponsor.
- No FDA Form-483 was issued. No major objectionable conditions noted.
- Data appear acceptable.

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/s/

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Khin U

8/27/03 09:07:24 AM

**Mille, Merril J**

---

**From:** Mille, Merril J  
**Sent:** Monday, June 09, 2003 2:15 PM  
**To:** 'Medley, Jim [PRDUS]'  
**Subject:** RE: NDA 21-615 Reminyl Extended Release Capsules



RE: NDA 21-615

Reminyl Extended

Dear Jim:

Your response to my question regarding the facility name and CFN was incomplete. We need the Establishment Registration Number (CFN) for the Pharmaceutical Sourcing Group, Americas (PSGA).

Please respond ASAP.  
Merril

My request of 15-MAY-2003 reads:

RE: N21-615

Please verify/clarify the manufacturing facilities name [Firm Name and Establishment Registration Number (CFN)] for Pharmaceutical Sourcing Group, Americas (PSGA)?

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/s/

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Merril Mille  
6/9/03 02:15:10 PM  
CSO

5/9/03

**NDA REGULATORY FILING REVIEW  
(Includes Filing Meeting Minutes)**

NDA **21-615**  
REMINYL (galantamine hydrochloride) Extended Release Capsules

Applicant: Johnson & Johnson Pharmaceutical Research & Development, L.C.C.

Date of Application: 24 FEB-2003  
Date of Receipt: 25-FEB-2003  
Date of Filing Meeting: 04-APR-2003  
Filing Date: 26-APR-2003                      FG Letter: 09-MAY-2003

Indication(s) requested: Treatment of mild to moderate dementia of the Alzheimer's type/

Type of Application: Full NDA   X   Supplement \_\_\_\_\_  
(b)(1)   X   (b)(2) \_\_\_\_\_  
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S   ✓   P \_\_\_\_\_  
Resubmission after a withdrawal or refuse to file \_\_\_\_\_  
Chemical Classification: (1,2,3 etc.)   3    
Other (orphan, OTC, etc.) \_\_\_\_\_

Has orphan drug exclusivity been granted to another drug for the same indication?      YES      NO   ✓  

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?  
YES                      NO

If the application is affected by the application integrity policy (AIP), explain.      N/A

User Fee Status: Paid   21-FEB-2003   Waived (e.g., small business, public health) \_\_\_\_\_  
Exempt (orphan, government) \_\_\_\_\_

Form 3397 (User Fee Cover Sheet) submitted: YES   ✓   NO \_\_\_\_\_

User Fee ID#   4501    
Clinical data? YES   ✓   NO \_\_\_\_\_ Referenced to NDA#   21-169    
Date clock started after UN   N/A  

User Fee Goal date:   25-DEC-2003  

Action Goal Date (optional) \_\_\_\_\_

- Does the submission contain an accurate comprehensive index?                      YES   ✓        NO
  - Form 356h included with authorized signature?                      YES   ✓        NO
- If foreign applicant, the U.S. Agent must countersign.**

- Submission complete as required under 21 CFR 314.50? YES [✓] NO  
 If no, explain:
  
- If electronic NDA, does it follow the Guidance? YES [✓] NO NA  
**If an electronic NDA: all certifications must be in paper and require a signature.**
  
- If Common Technical Document, does it follow the guidance? YES [✓] NO  
 NA
  
- Patent information included with authorized signature? YES [✓] NO
  
- Exclusivity requested? YES; If yes, ✓[years not stated] years NO  
 Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.
  
- Correctly worded Debarment Certification included with authorized signature? YES [✓] NO  
**If foreign applicant, the U.S. Agent must countersign.**

Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that ✓ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix \_\_\_\_." Applicant may not use wording such as, "To the best of my knowledge, ...."

- Financial Disclosure included with authorized signature? YES [✓] NO  
 (Forms 3454 and/or 3455)  
**If foreign applicant, the U.S. Agent must countersign.**
  
- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO  
 If no, for what ages and/or indications was a waiver and/or deferral requested:
  
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES [✓] NO

**Refer to 21 CFR 314.101(d) for Filing Requirements**

PDUFA and Action Goal dates correct in COMIS? YES NO [✓]

If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers:

End-of-Phase 2 Meeting? Date \_\_\_\_\_ NO  
 If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s) 11/26/02 NO  
 If yes, distribute minutes before filing meeting.

**Project Management**

- Copy of the labeling (PI) sent to DDMAC? YES X NO
- Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?  
X YES NO
- MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?  
 YES NO X NA
- OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support?  
 YES NO X NA  
 NA
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ X NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?  
 YES NO X NA

**Chemistry**

- Did sponsor request categorical exclusion for environmental assessment? X YES NO  
 If no, did sponsor submit a complete environmental assessment? YES NO  
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) package submitted? X YES NO
- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO X NA

**If 505(b)(2), complete the following:**

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?  
 (Normally, FDA will refuse-to-file such applications.)

YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?

If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

*If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.
- 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?  
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  
YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11-APR-2003

BACKGROUND

Reminyl Tablets and oral solution were previously approved under NDAs 21-169 and 21,224, respectively. .  
 The subject NDA (21-615) provides for an extended-release formulation.

ATTENDEES:

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical Team Leader	Armando Oliva, M.D.
Secondary Medical:	Ranji Mani, M.D.
Statistical Team Leader	Kun Jin, Ph.D.:
Statistical Reviewer	Kun He, Ph.D.
Pharmacology:Supervisor:	Barry Rosloff, Ph.D.
Pharmacology Reviewer:	Ikram Elayan, Ph.D.
Statistical Pharmacology:	
Chemist Team Leader:	:Maryla Guzewska, Ph.D.
Chemistry Reviewer:	Waclaw Rzeszotarski, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutics Team Leader	Raman Baweja, Ph.D.
Biopharmaceutical:	Ronald Kavanaugh, Ph.D.
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Nih Khin, M.D.
Project Manager:	Merril J.Mille,R.Ph.
Other Consults: DDMAC	Lisa Stockbridge,

Per reviewers, all parts in English, or English translation? YES X NO    

CLINICAL - File   X   Refuse to file           

• Clinical site inspection needed: YES   X   NO           

MICROBIOLOGY CLINICAL - File            Refuse to file           

STATISTICAL - File   X   Refuse to file           

BIOPHARMACEUTICS -- File   X   Refuse to file           

• Biopharm. inspection Needed: YES   X   NO           

PHARMACOLOGY - File   X   Refuse to file

CHEMISTRY –

Establishment(s) ready for inspection? YES  NO  File  Refuse to file

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

The application is unsuitable for filing. Explain why:

Merrill J. Mille, R.Ph.  
Consumer Safety Officer, HFD-120

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/s/

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Merril Mille  
5/9/03 03:13:15 PM

**Mille, Merrill J**

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**From:** Mille, Merrill J  
**Sent:** Friday, May 09, 2003 3:25 PM  
**To:** 'Medley, Jim [PRDUS]'  
**Subject:** NDA 21-615 Reminyl Extended Release Capsules

1. No new deficiencies issues were identified during the filing meeting.
2. The consult on the nomenclature regarding the acceptability of "ER" has not been completed as of this day.

Have a great week-end.

Merril

*Merril Mille, R.Ph.*  
Consumer Safety Officer  
Div. of Neuropharmacological Drug Products, HFD-120  
CDER, FDA  
301-594-5528 (phone)  
301-594-2859 (fax)  
millem@cder.fda.gov

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/s/

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Merril Mille  
5/9/03 03:22:47 PM  
CSO