021-615_ORIG_APPROVAL_PKG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 21-615

Trade Name:	Razadyne (formerly Reminyl) ER Capsules
Generic Name(s):	(galantamine Hydrobromide)
Sponsor:	Johnson & Johnson Pharmaceutical Research, Inc.
Agent:	
Approval Date:	December 22, 2004

Indication: Provides for a controlled-release formulation

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-615

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Statistical Review(s)	X
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-615

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-615

Johnson & Johnson Pharmaceutical Research and Development, LLC
Attention: Susan Merchant
1125 Trenton Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Ms. Merchant:

Please refer to your new drug application (NDA) dated February 24, 2003, received February 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for galantamine hydrobromide extended release capsules, 8, 16, and 24 mg.

On December 22, 2004, FDA issued a letter stating that the NDA was approved. By today's letter the approval date for NDA 21-615 is revised to April 1, 2005. The reasons for this action are described below.

In a November 11, 2005 letter to Russell Katz, MD, Director, Division of Neurology Products, you requested that FDA revise the approval date for this NDA from December 22, 2004, to April 1, 2005. This request was based upon the fact that it was not until the later date that FDA and Johnson and Johnson (J&J) agreed upon the new trade name (Razadyne) for the product. As your letter noted, FDA's December 22, 2004 action letter stated that, because of medication errors associated with the use of the trade name Reminyl for the approved galantamine hydrobromide immediate release product, J & J would not market the extended release product until a new trade name had been reviewed and approved by FDA.

We have reviewed your letter and the NDA record, and concluded that the action letter of December 22, 2004, should be considered an approvable letter as described in 21 CFR 314.110. In light of the concerns about medication errors expressed in that letter, it is reasonable to conclude that Razadyne ER was not approved until April 1, 2005, when the Agency completed its review of the proposed new trade name, found it acceptable, and conveyed this information to J&J.

In light of this determination, we will be amending our records to identify April 1, 2005, as the approval date for NDA 21-615. In addition, the Orange Book will be changed to reflect this approval date.

If you have any questions, call Melina Griffis, R.Ph., Regulatory Project Manager, at 301-796-1078.

Sincerely,

{See appended electronic signature page}

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

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/s/

Robert Temple

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-615

Johnson & Johnson Pharmaceutical Research
Attention: James H. Medley, Ph.D.
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

Dear Dr. Medley:

Please refer to your new drug application (NDA) dated February 24, 2003, received February 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reminyl (galantamine hydrobromide) Extended Release Capsules, 8, 16, and 24 mg.

We acknowledge receipt of your submissions dated October 27, 2004, December 3, 2004 and December 17, 2004.

The October 27, 2004 submission constituted a complete response to our July 27, 2004 action letter.

This new drug application provides for a controlled release formulation of galantamine hydrobromide.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the attached agreed-upon labeling text.

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

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission as "**FPL for approved NDA 21-615**". Approval of this submission by FDA is not required before the labeling is used.

We note your commitment to change the name of your Reminyl products, because of the recent medication errors associated with Reminyl and Amaryl. We also note your commitment to adopt a new name for the controlled release formulation prior to its marketing, and to submit the new proposed proprietary names to the Agency for our review prior to implementation. Because you have not yet submitted a new name for the controlled release formulation, it is being approved without a tradename.

We note that you have agreed to adopt the following interim dissolution method and specifications for all strengths of Galantamine HBr Modified Release Capsules.

(b) (4)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitment in your submission dated December 17, 2004. The commitment is listed below.

> We commit to provide additional dissolution data within 6 months of approval to set final dissolution specifications. This additional data will include:
>
> - Samples at the following times 1, 4, 8, 10, 11, and 12 hours.
> - Content Uniformity data.

Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates and any changes in plans since the last annual report. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence.**"

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Melina Griffis, R.Ph., Regulatory Project Manager, at (301) 594-5526.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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/s/

Robert Temple
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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-615

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-615

Johnson & Johnson Pharmaceutical Research
Attention: James H. Medley, Ph.D.
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

Dear Dr. Medley:

Please refer to your new drug application (NDA) dated February 24, 2003, received February 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reminyl (galantamine hydrobromide) Extended Release Capsules, 8, 16, and 24 mg.

We acknowledge receipt of your submission dated:

April 28, 2003	May 6, 2003	June 19, 2003
September 29, 2003	October 3, 2003	November 14, 2003
November 21, 2003		

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Lack of Substantial Evidence of Effectiveness:

The supporting clinical efficacy study GAL-INT-10 fails to provide evidence of effectiveness of extended-release galantamine.

As you know, the current regulatory standard for a demonstration of effectiveness for treatments of Alzheimer's Disease is the showing of statistically significant superiority to placebo on both of two co-primary efficacy measures: a cognitive measure and a global/functional measure. Unfortunately, Reminyl ER was not shown to be superior to placebo on the CIBIC-Plus (for the intent-to-treat population on the last observation carried forward analysis, the between-treatment contrast yields p=0.22). Thus, based on the pre-specified primary efficacy analysis, this study must be considered not to have shown substantial evidence of effectiveness of Reminyl® Extended-Release Capsules.

While the between-treatment comparison on the ADCS-ADL, a secondary efficacy measure that also can be acceptable as a co-primary measure of overall functioning (when so designated prospectively), was nominally significant ($p<0.001$), the negative finding on the protocol specified global measure (the CIBIC-Plus) makes relying on any analysis of further outcome variables inappropriate, because to do so inflates the overall Type I error for the study.

Before this application can be approved, you must submit a single adequate and well-controlled investigation that demonstrates superiority of Reminyl ER to placebo on two prospectively designated outcomes of the sort described above.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division/ the Division of Neuropharmacological Drug Products to discuss what steps need to be taken before the application may be approved.

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

If you have any questions, contact Melina Griffis, Senior Regulatory Project Manager, at (301) 594-5526

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7/27/04

NDA 21-615

Johnson & Johnson Pharmaceutical Research
Attention: James H. Medley, Ph.D.
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

Dear Dr. Medley:

Please refer to your new drug application (NDA) dated February 24, 2003, received February 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reminyl (galantamine hydrobromide) Extended Release Capsules, 8, 16, and 24 mg.

We acknowledge receipt of your submissions dated May 27, 2004 and June 11, 2004.

The May 27, 2004 submission constituted a complete response to our December 23, 2003 action letter.

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

You have presented numerous post hoc re-analyses of the CIBIC-Plus, all of which achieve nominal significance, and which you suggest establish that Reminyl ER is stastically significantly superior to placebo on this outcome measure. However, we believe that it is inappropriate to rely on the results of post hoc analyses unless a compelling argument can be made for disregarding the protocol-specified analyses (as we noted in our December 23, 2003 letter, relying on additional analyses in the face of a negative result on the primary analysis inflates the Type I error for the study). We do not believe that you have provided any convincing rationale for considering the protocol-specified analysis of the CIBIC-Plus to be inappropriate, and, therefore, replaceable by other analyses. Indeed, the protocol-specified analysis of this outcome measure was standard for this measure, and was reasonable in all fundamental aspects. The fact that you have identified numerous other analyses of this outcome measure that you believe, after the fact, are more appropriate, does not constitute, in our view, sufficient justification for rejecting the results of the original analysis. Therefore, given our view that the protocol-specified analysis was sound, we consider it inappropriate to accept as definitive analyses done retrospectively, after a non-significant finding on the original analysis.

Further, even if we were convinced that the protocol-specified analysis of the CIBIC-Plus was inappropriate, the alternative analyses you performed are not clearly appropriate on their own terms. For example, in the analysis in which you stratified by study site, you adopted a rule for pooling small centers that, in addition to being obviously unplanned (and therefore only one of many possible pooling schemes), was itself problematic, given that it resulted in a single "center" that was much

larger than any other center in the study. The creation of this very large single "center" could have tended to obscure the effects of center in the analysis. Similarly, you have not adequately justified the appropriateness of the several other specific analyses you have performed, given the extraordinarily large number of analyses that could have been performed.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you have any questions, contact Melina Griffis, R.Ph., Senior Regulatory Project Manager, at (301) 594-5526.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
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