



NDA 21-169/S-011
NDA 21-224/S-009
NDA 21-615/S-002

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

Dear Ms. Merchant:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for galantamine hydrobromide Tablets, Oral Solution and Extended-Release Capsules.

We acknowledge receipt of your submissions dated March 18, 2005, April 6, 2005 and April 13, 2005.

These supplemental new drug applications provide for a new section to be added to the Precautions section of labeling describing results of two studies conducted in subjects with mild cognitive impairment. The specific agreed upon language reads as follows:

Deaths in Subjects with Mild Cognitive Impairment (MCI)

In two randomized placebo controlled trials of 2 years duration in subjects with mild cognitive impairment (MCI), a total of 13 subjects on REMINYL® (n=1026) and 1 subject on placebo (n=1022) died. The deaths were due to various causes which could be expected in an elderly population; about half of the REMINYL® deaths appeared to result from various vascular causes (myocardial infarction, stroke, and sudden death).

Although the difference in mortality between REMINYL® and placebo-treated groups in these two studies was significant, the results are highly discrepant with other studies of REMINYL®. Specifically, in these two MCI studies, the mortality rate in the placebo-treated subjects was markedly lower than the rate in placebo-treated patients in trials of REMINYL® in Alzheimer's disease or other dementias (0.7 per 1000 person years compared to 22-61 per 1000 person years, respectively). Although the mortality rate in the REMINYL®-treated MCI subjects was also lower than that observed in REMINYL®-treated patients in Alzheimer's disease and other dementia trials (10.2 per 1000 person years compared to 23-31 per 1000 person years, respectively), the relative difference was much less. When the Alzheimer's disease and other dementia studies were pooled (n=6000), the mortality rate in the placebo group numerically exceeded that in the REMINYL® group. Furthermore, in the MCI studies,

no subjects in the placebo group died after 6 months, a highly unexpected finding in this population.

Individuals with mild cognitive impairment demonstrate isolated memory impairment greater than expected for their age and education, but do not meet current diagnostic criteria for Alzheimer's disease.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the submitted labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert dated April 13, 2005).

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 "**FPL for approved supplement NDA 21-169/S-011, NDA 21-224/S-009 and NDA 21-615/S-002.**" Approval of these submissions by FDA is not required before the labeling is used.

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}

Russell Katz, M.D.

Director

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz

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