DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Victoria M. Wagner-Weber
Assistant Director, Regulatory Affairs
Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

Re: NDA 21-169
Reminyl (galantamine HBr)
MACMIS # 10722

Dear Ms. Wagner-Weber:

Through routine monitoring and surveillance, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional materials (01-RM-210, 01-RM-213) for Reminyl (galantamine HBr) that are misleading and in violation of the Federal Food, Drug, and Cosmetic Act and applicable regulations.

Specifically, DDMAC objects to the following:

1. Claims or representations that Reminyl is safe and effective for the treatment of Alzheimer's patient subgroups with probable vascular dementia are misleading because they suggest a specific benefit linked to the vascular dementia when none has been demonstrated. Specifically, as all patients in the study relied on had Alzheimer's Disease for which Reminyl is effective, the fact that they also may have had another disease is not of clear relevance. Put another way, the patients should have responded to the Alzheimer's treatment whether or not they had another disease. The effectiveness of Reminyl for the claimed new use has not been demonstrated by substantial evidence or substantial clinical experience. Examples of the misleading claims include

   - a two-page spread in the slim jim detail aid (01-RM-213, pages 6-7) entitled "New Data Available: Alzheimer's Disease with Cerebrovascular Disease and Probable Vascular Dementia" presenting four graphs that depict positive results in cognition, global function, activities of daily living (ADLs), and behavior.

   - the front of a fact card (01-RM-210) and pages 2-3 of the slim jim (01-RM-213), entitled "All Around Benefits," that state that there were "2 patient types studied" with Reminyl. A second bullet under this headline indicates that the second group includes "AD with cerebrovascular disease and probable vascular dementia" representing "82% of all dementia patients." An accompanying pie chart emphasizes the importance of this second group.

The study referenced to support these claims (GAL-INT-6) is inadequate for several reasons. First, the patient population subgroups labeled "probable vascular dementia" and "cerebrovascular disease" (or "mixed dementia") have not been shown to be clinically distinct populations from Alzheimer's Disease. Second, apart from whether such a demonstration would have been meaningful, Reminyl did not in fact demonstrate efficacy in the "probable vascular dementia" subgroup. Evidence of efficacy was seen in the "mixed dementia" subgroup, but, as noted above, the co-existing Alzheimer's Disease in this subgroup may have accounted for all of the benefit seen in the study. As you know, [ ] submitted a supplemental new drug application for [ ] seeking [ ]

2. The front of the fact card and page 3 of the slim jim also state that Reminyl is a "unique agent with consistent results." This claim is misleading because it implies that Reminyl is distinct in its properties from other acetylcholinesterase inhibitors demonstrated to be safe and effective for the treatment of mild to moderate Alzheimer's disease. As a new molecular entity, of course, galantamine has a unique structure. However, there are pharmacologically similar products that have the same indications.

To address these objections, DDMAC requests that Janssen do the following:

1. Immediately discontinue the use of these and any other promotional material or activities with the same or similar issues.

2. Respond to this letter within ten days. Your response should include a statement of your intent to comply with the above, a list of all promotional materials and activities with the same or similar issues, and your methods for discontinuing their use.

If you have any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #10722 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Lisa L. Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing,
Advertising and Communications

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

/s/

Lisa Stockbridge
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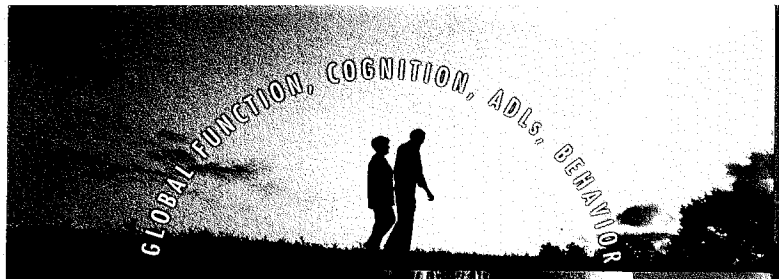


REMINYL

2 PATIENT TYPES STUDIED[1-4]

4 IMPORTANT OUTCOME MEASURES[1,2]

1 UNIQUE AGENT WITH CONSISTENT RESULTS[1-4]

References: 1. Tariot PN et al. *Neurology.* 2000;54:2269-2276. **2.** Data on file, Janssen. **3.** Wilcock GK et al. *BMJ.* 2000;321:1-7. **4.** Raskind MA et al. *Neurology.* 2000;54:2261-2268. **5.** Maelicke A et al. *Eur J Pharmacol.* 2000;393:65-170. **6.** Samochocki et al. *Actu Neurol Scand.* 2000:176:68-73. **7.** *2001 Red Book® Update.* November 2001;20(11). **8.** *PriceAlert™.* November 15, 2001.

Reminyl®
galantamine HBr Tablets and Oral Solution

www.reminyl.com

Please see full prescribing information enclosed.

 Printed in U.S.A. 01-RM-213 02A7837 December 2001

JANSSEN PHARMACEUTICA PRODUCTS, L.P.
Titusville, NJ 08560-0200

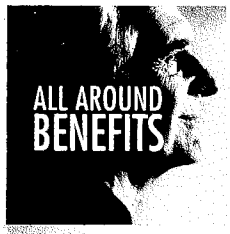
ORTHO-McNEIL
Ortho-McNeil Pharmaceutical, Inc.
Raritan, NJ 08869-0602

helping you help the one you care for
SharingCare

ALL AROUND SUCCESS WITH REMINYL®
(galantamine HBr)

IN MILD TO MODERATE ALZHEIMER'S DISEASE (AD)

NEW DATA ENCLOSED

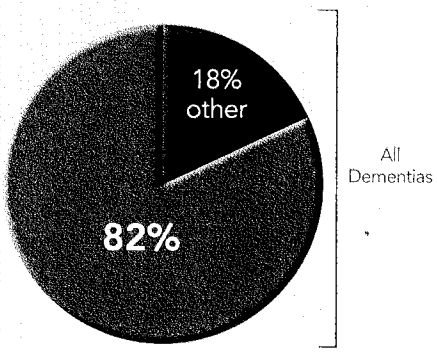


REMINYL

FOR MILD TO MODERATE DEMENTIA OF THE ALZHEIMER'S TYPE

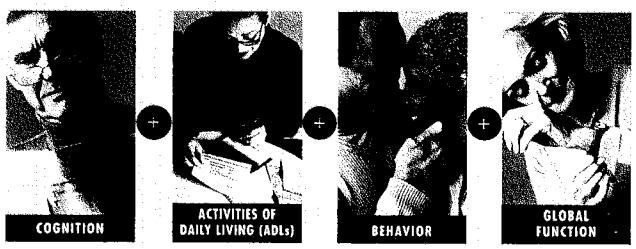
2 PATIENT TYPES STUDIED

- Mild to moderate Alzheimer's disease (AD)[1-4]
- AD with cerebrovascular disease and probable vascular dementia[2]
  - — These patient types account for 82% of all dementia patients[2]



4 IMPORTANT OUTCOME MEASURES[1,2]

- REMINYL results were statistically significant vs placebo on all 4 outcome measures[1,2]



1 UNIQUE AGENT WITH CONSISTENT RESULTS[1-4]

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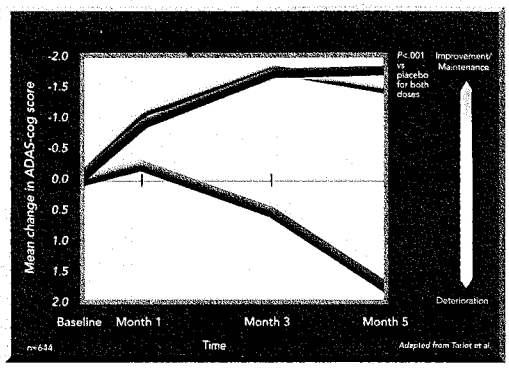
Reminyl®
galantamine HBr Tablets and Oral Solution

ALZHEIMER'S DISEASE (AD)[1-3]

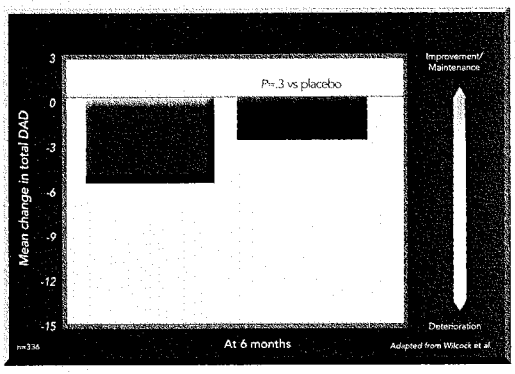
2

COGNITION*



Placebo n=225 | REMINYL 16 mg/day n=208 | REMINYL 24 mg/day n=211

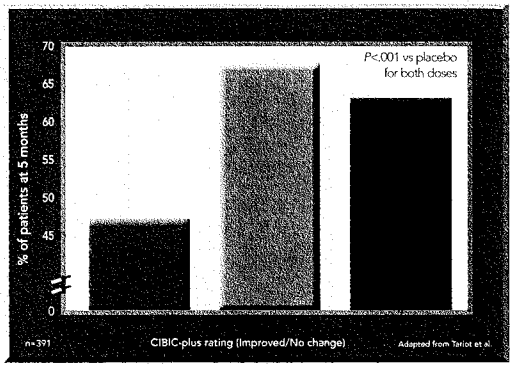
ADLs†



Placebo n=177 | REMINYL 24 mg/day n=159

4

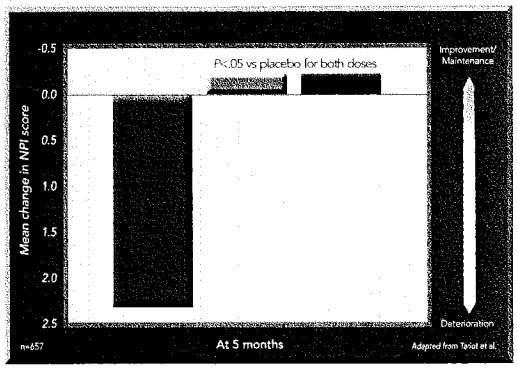
GLOBAL FUNCTION*



Placebo n=112 | REMINYL 16 mg/day n=143 | REMINYL 24 mg/day n=136

1

BEHAVIOR*



Placebo n=234 | REMINYL 16 mg/day n=211 | REMINYL 24 mg/day n=212

* A 5-month, multicenter, double-blind, randomized, placebo-controlled trial of 978 patients with mild to moderate AD. Observed case (OC) analyses shown. Cognition and global function were primary endpoints; ADLs and behavior were secondary endpoints.

† A 6-month, multicenter, double-blind, randomized, placebo-controlled trial of 653 patients with mild to moderate AD. OC analyses shown. Cognition and global function were primary endpoints; ADLs were a secondary endpoint.

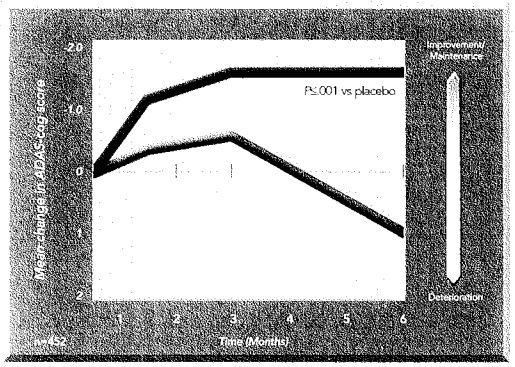
Please see full prescribing information enclosed.

Reminyl® galantamine HBr Tablets and Oral Solution

ALZHEIMER'S DISEASE WITH CEREBROVASCULAR DISEASE AND PROBABLE VASCULAR DEMENTIA[2]

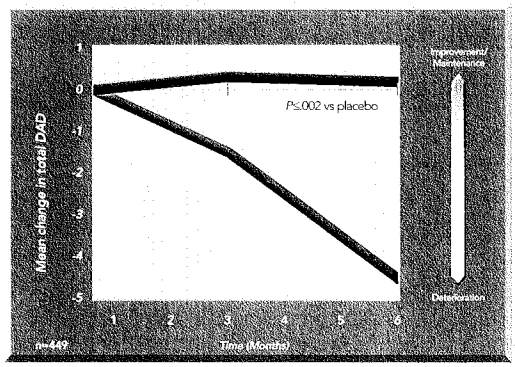
A 6-month, multicenter, double-blind, placebo-controlled trial of 592 patients with AD with cerebrovascular disease and probable vascular dementia. OC analyses shown. Cognition and global function were primary endpoints; ADLs and behavior were secondary endpoints. REMINYL dose was escalated weekly in increments of 4 mg/day to the study dose of 24 mg/day.

COGNITION



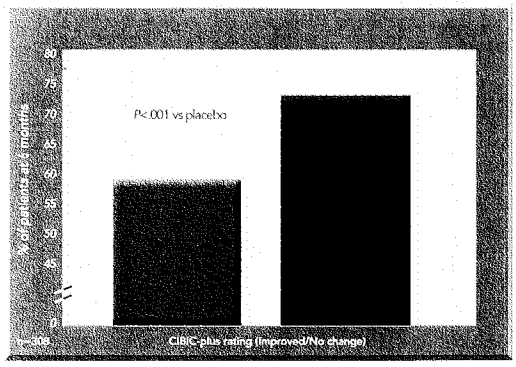
Placebo n=162 — REMINYL 24 mg/day n=290

ADLs



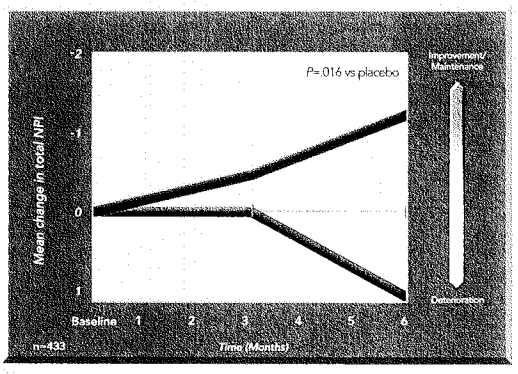
Placebo n=161 — REMINYL 24 mg/day n=288

GLOBAL FUNCTION



Placebo n=95 — REMINYL 24 mg/day n=213

BEHAVIOR



Placebo n=154 — REMINYL 24 mg/day n=279

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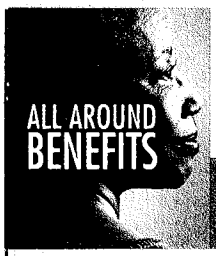
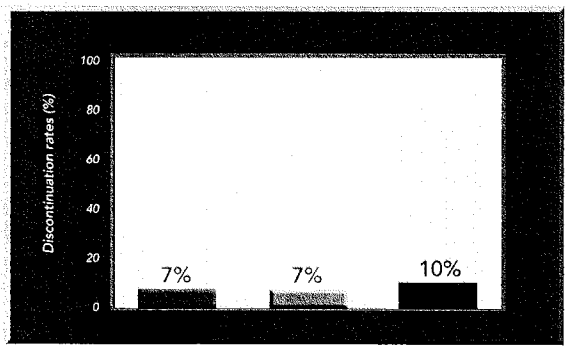


PROVEN SAFETY AND TOLERABILITY

Low discontinuation rates comparable with placebo



A 5-month, multicenter, double-blind, randomized, placebo-controlled trial of 978 patients with mild to moderate AD. A 4-week dose-escalation schedule was used for patients taking REMINYL.

Adverse events were generally mild and transient

- The most frequent adverse events that occurred with placebo, REMINYL 16 mg/day, and REMINYL 24 mg/day, respectively, were nausea (5%, 13%, 17%), vomiting (1%, 6%, 10%), diarrhea (6%, 12%, 6%), anorexia (3%, 7%, 9%), and weight loss (1%, 5%, 5%)
- For patients who experienced adverse events, the majority occurred during the dose-escalation phase

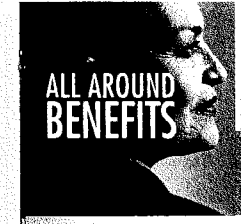
MECHANISM OF ACTION

REMINYL is a competitive and reversible agent that enhances cholinergic function

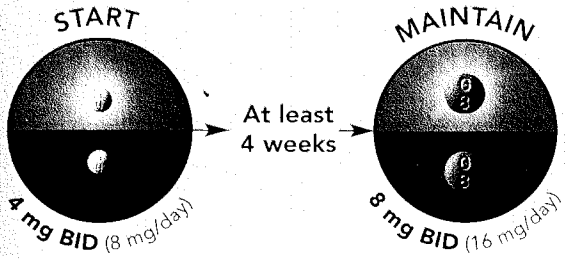
- The precise mechanism of action is unknown but is thought to include acetylcholinesterase inhibition
  - Clinical significance of this mechanism is unknown
- In addition, it is postulated that REMINYL is a modulator of nicotinic receptors[5,6]
  - Clinical significance of this mechanism is unknown

Please see full prescribing information enclosed.

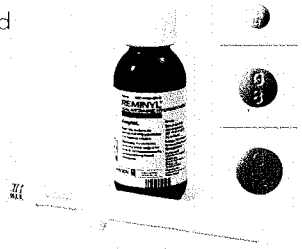
Reminyl® galantamine HBr Tablets and Oral Solution



SIMPLE ONE-STEP DOSE ESCALATION



- Take with morning and evening meals. Patients may be given REMINYL 12 mg BID (24 mg/day) after at least 4 weeks at the 16-mg/day dose based on assessment of clinical benefit and tolerability
- Patients with moderate hepatic impairment or moderate renal impairment should not exceed 16 mg/day. REMINYL is not recommended in patients with severe renal or hepatic impairment
- REMINYL is available in 4-mg, 8-mg, and 12-mg tablets and oral solution



Added flexibility of oral solution

- REMINYL oral solution (4 mg/mL): Start patients on 1 mL BID for at least 4 weeks. Then escalate to the maintenance dose of 2 mL BID
  - —REMINYL oral solution offers the same flexibility as REMINYL tablets to go to 24 mg/day, given as 3 mL BID after at least 4 weeks at the previous dose

COMPETITIVELY PRICED

REMINYL may offer a cost advantage compared with other acetylcholinesterase inhibitors[7,8]

	Tablets	AWP
REMINYL®*	30-day supply	$129.60
Aricept®†	30-day supply	$134.54
Exelon®‡	30-day supply	$134.14

	Oral Solution	AWP
REMINYL	4 mg/mL (100 mL bottle)	$144.00
Exelon	2 mg/mL (120 mL bottle)	$246.96

Average wholesale price (AWP) provided by *Red Book® Update*, November, 2001, and *PriceAlert*™, November, 2001. Actual pharmacy or out-of-pocket costs may differ.

* REMINYL is available in 4-mg, 8-mg, and 12-mg tablets.

† Aricept (donepezil) is available in 5-mg and 10-mg tablets and is a registered trademark of Eisai Co., Ltd.

‡ Exelon (rivastigmine) is available in 1.5-mg, 3-mg, 4.5-mg, and 6-mg tablets and is a registered trademark of Novartis Pharmaceuticals.

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REMINYL

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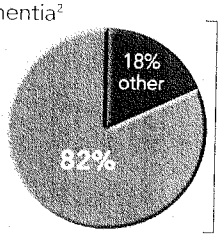
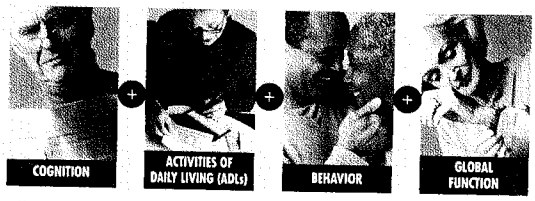


4 IMPORTANT OUTCOME MEASURES[1,2]



- REMINYL results were statistically significant vs placebo on all 4 outcome measures[1,2]

1 UNIQUE AGENT WITH CONSISTENT RESULTS[1-4]

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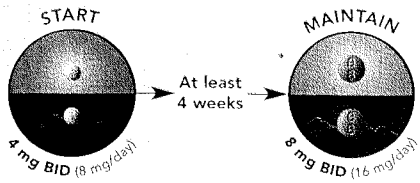
Simple, 1-step dose escalation



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- Patients with moderate hepatic impairment or moderate renal impairment should not exceed 16 mg/day. REMINYL is not recommended in patients with severe renal or hepatic impairment
- REMINYL is available in 4-mg, 8-mg, and 12-mg tablets and oral solution (4 mg/mL)

Please see enclosed full prescribing information.

www.reminyl.com

Reminyl®
galantamine HBr Tablets and Oral Solution

References: 1. Tariot PN et al. *Neurology.* 2000;54:2269-2276. **2.** Data on file, Janssen. **3.** Wilcock GK et al. *BMJ.* 2000;321:1-7. **4.** Raskind MA et al. *Neurology.* 2000;54:2261-2268.

 Printed in U.S.A. 01-RM-210 02A7833 December 2001

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