Question 8

In the RCTs, please examine the frequency of heart rate and rhythm AEs among patients taking both digoxin and galantamine, digoxin alone, galantamine alone, and neither drug. Please also perform mean change from baseline and outlier analyses for heart rate as measured on vital signs and ECG and for PR interval as measured on ECG for the groups designated above. In a separate analysis, please repeat the above analysis, but examine patients taking beta blockers, verapamil, or diltiazem. Finally, please repeat the original analysis combining the digoxin users with the users of beta blockers, verapamil, or diltiazem.

The sponsor used pooled AE data from the NDA controlled trials USA-1, INT-1 and USA-10 to compare cardiovascular AE risk for the drug combinations mentioned above. The sponsor relied on data from study USA-10 to analyze mean changes for heart rate and PR interval changes for the different treatment groups. The mean change analyses subtracted the endpoint value from the baseline value for vital sign heart rate, ECG heart rate, and PR interval. The sponsor commented that their heart rate and PR interval outlier analyses identified 1 or fewer outliers per treatment group and so these results were not further summarized. Summaries of the sponsor's analyses are included in Tables 2 (pulse, heart rate, and PR interval data) and 3 (AE data).

Digoxin (D)

Cardiovascular AEs

The sponsor concluded that there were no imbalances in cardiovascular AEs, particularly for bradycardia, AV block, or syncope, when comparing patients taking digoxin and galantamine to those receiving galantamine alone. The risk for bradycardia was the same for the G group and the D+G group (2.6% each [38/1475] and [2/78], respectively) and higher than the D group (0/33) or the N group (0.7% [5/681]). With few identified events, the sponsor was unable to discern any differences in risk for the remaining cardiovascular AEs.

Heart Rate, PR Interval

There did not appear to be notable differences in mean change from baseline for heart rate or PR interval for the D+G group compared to G group. In study USA-10, the mean change from baseline for heart rate using pulse was 0.1 bpm for the D+G group compared to –2.4 bpm for the G group, -0.7 bpm for the D group and -0.9 bpm for the N group. The mean change from baseline for heart rate using ECG was –3.0 bpm for the D+G group compared to –2.8 bpm for the G group, -2.3 bpm for the D group and -0.9 bpm for the N group. The PR interval mean change from baseline was 2.6msec for the D+G group compared to 3.1msec for the G group, -0.8msec for the D group and –2.1msec for the N group.

β-blockers (B)

Cardiovascular AEs

The sponsor found an increased risk of bradycardia AEs in patients taking B+G compared to those receiving galantamine alone but similar risks for falls and syncope. The risk for bradycardia for the B+G group was 6.9% (16/231) compared to 1.8% (24/1322) for the galantamine group, 2.2% (2/92) for the β-blocker alone group and 0.5% (3/622) for the N group. Although not as marked as for bradycardia, there was some excess risk of AV block in the B+G group (1.3%, 3/231) compared to the G group (0.5%, 7/1322), the B group (0/92), and the N group (0.3%, 2/622).

Heart Rate, PR Interval

There did not appear to be evidence of increased risk for decrease in heart rate or prolongation of PR interval for the B+G group compared to the G group based on the mean change from baseline data. In study USA-10, the mean change from baseline for heart rate using pulse was –1.3 bpm for the B+G group compared to –2.4 bpm for the G group, 0.1 bpm for the B alone group and –1.1 bpm for the N group. The mean change from baseline for heart rate using ECG was –1.7 bpm for the B+G group compared to –3.1 bpm for the G group, -2.2 bpm for B alone group and –0.8 bpm for the N group. The PR interval mean change from baseline was 0.2 msec for the B+G group compared to 3.6msec for the G group, -2.2 msec for the B alone group and 2.7 msec for the N group.

Verapamil (V)

Cardiovascular AEs

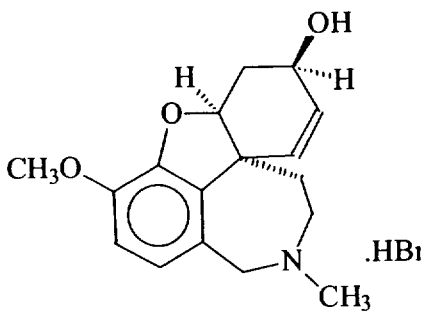
The sponsor found no notable differences in risk for cardiovascular AEs for the V+G group compared to the G group but the data suggested increased risk for syncope and falls in the V+G group. The risk for syncope in the V+G group was 8.2% (4/49) compared to 2.1% (32/1504) in the G group, 0/21 in the V alone group, and 0.9% (6/693) in the N group. The risk for falls in the V+G group was 10.2% (5/49) compared to 5.5% (82/1504) in the G group, 9.5% (2/21) in the V alone group, and 5.2% (36/693) in the N group.

Heart Rate, PR Interval

There did not appear to be consistent evidence of increased risk for a notable decrease in heart rate or prolongation of PR interval for V+G compared to the G group based on the mean change from baseline data. Although the ECG data on heart rate showed more slowing of the heart rate in the V+G group compared to the G group, this observation was not supported by the pulse data. In study USA-10, the mean change from baseline for heart rate using ECG was –5.4 bpm for the V+G group compared to –2.8 bpm for the G group, 1.6 bpm for the V alone group and –0.8 bpm for the N group. The mean change from baseline for heart rate using pulse was –2.9 bpm for the V+G group compared to –2.2 bpm for the G group, -1.0 bpm for the V alone group and –0.9 bpm for the N group. The PR interval mean change from baseline was –5.0 msec for the V+G group compared to 3.3msec for the G group, 1.6 msec for the V alone group and 2.0 msec for the N group.

DESCRIPTION

REMINYL® (galantamine hydrobromide), extracted from the bulbs of the daffodil, *Narcissus pseudonarcissus*, is a reversible, competitive acetylcholinesterase inhibitor. It is known chemically as (4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide. It has an empirical formula of $C_{17}H_{21}NO_3$ ·HBr and a molecular weight of 368.27. Galantamine hydrobromide is a white to almost white powder and is sparingly soluble in water. The structural formula for galantamine hydrobromide is:



REMINYL® for oral use is available in circular biconvex film-coated tablets of 4 mg (off-white), 8 mg (pink, scored), and 12 mg (orange-brown). Each 4, 8, and 12 mg (base equivalent) tablet contains 5.126, 10.253, and 15.379 mg of galantamine hydrobromide, respectively. Inactive ingredients include colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, propylene glycol, talc, and titanium dioxide. The 4 mg tablets contain yellow ferric oxide. The 8 mg tablets contain red ferric oxide. The 12 mg tablets contain red ferric oxide and FD&C yellow #6 aluminum lake.

CLINICAL PHARMACOLOGY

Mechanism of Action

Although the etiology of cognitive impairment in Alzheimer's disease (AD) is not fully understood, it has been reported that acetylcholine-producing neurons degenerate in the brains of patients with Alzheimer's Disease. The degree of this cholinergic loss has been correlated with degree of cognitive impairment and density of amyloid plaques (a neuropathological hallmark of Alzheimer's Disease).

Galantamine, a tertiary alkaloid, is a competitive and reversible inhibitor of acetylcholinesterase. While the precise mechanism of galantamine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this mechanism is correct, galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that galantamine alters the course of the underlying dementing process.

Pharmacokinetics

Galantamine is well absorbed with absolute oral bioavailability of about 90%. It has a terminal elimination half life of about 7 hours and pharmacokinetics are linear over the range of 8-32 mg/day.
The maximum inhibition of anticholinesterace activity of about 40 % was achieved about one hour after a single oral dose of 8 mg galantamine in healthy male subjects.

Absorption and Distribution

Galantamine is rapidly and completely absorbed with time to peak concentration about 1 hour. Bioavailability of the tablet was the same as the bioavailibility of an oral solution. Food did not affect the AUC of galantamine but C_{max} decreased by 25 % and T_{max} was delayed by 1.5 hours. The mean volume of distribution of galantamine is 175 L.

The plasma protein binding of galantamine is 18 % at therapeutically relevant concentrations. In whole blood, galantamine is mainly distributed to blood cells (52.7%). The blood to plasma concentration ratio of galantamine is 1.2.

Metabolism and Elimination

Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. *In vitro* studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly (see **PRECAUTIONS, DRUG-DRUG INTERACTIONS**). O-demethylation, mediated by CYP2D6 was greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity.

In studies of oral ^{3}H-galantamine, unchanged galantamine and its glucuronide, accounted for most plasma radioactivity in poor and extensive CYP2D6 metabolizers. Up to 8 hours post-dose, unchanged galantamine accounted for 39-77% of the total radioactivity in the plasma, and galantamine glucuronide for 14-24%. By 7 days 93-99% of the radioactivity had been recovered, with about 95 % in urine and about 5% in the feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32 % of the dose and that of galantamine glucuronide for another 12% on average.

After i.v. or oral administration, about 20% of the dose was excreted as unchanged galantamine in the urine in 24 hours, representing a renal clearance of about 65 mL/min., about 20-25% of the total plasma clearance of about 300 mL/min.

Special Populations

CYP2D6 poor metabolizers

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar C_{max} and about 35% AUC_{∞} increase of unchanged galantamine compared to extensive metabolizers.

A total of 356 patients with Alzheimer's disease enrolled in two phase 3 studies were genotyped with respect to CYP2D6 (n=210 hetero-extensive metabolizers, 126 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability.

Hepatic Impairment – Following a single 4 mg dose of galantamine, the pharmacokinetics of galantamine in subjects with mild hepatic impairment (n=8; Child-Pugh score of 5-6) were similar to those in healthy subjects. In patients with moderate hepatic impairment (n=8; Child Pugh score of 7-9), galantamine clearance was decreased by about 25 % compared to normal volunteers. Exposure would be expected to increase further with increasing degree of hepatic impairment (see **PRECAUTIONS and DOSAGE and ADMINISTRATION).**

Renal Impairment – Following a single 8 mg dose of galantamine, AUC increased by 37 % and 67 % in moderate and severely renal-impaired patients compared to normal volunteers. (See **PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

Elderly - Data from clinical trials in patients with Alzheimer's Disease indicate that galantamine concentrations are 30-40% higher than in healthy young subjects.

Gender and Race- No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of REMINYL®, but a population pharmacokinetic analysis indicates (n= 539 males and 550 females) that galantamine clearance is about 20% lower in females than in males (explained by lower body weight in females) and race (n= 1029 white, 24 black, 13 Asian and 23 other) did not affect the clearance of Reminyl®.

Drug-Drug Interactions

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on in vitro studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide. Galantamine is also glucuronidated and excreted unchanged in urine.

(A) Effect of other drugs on the metabolism of REMINYL®: Drugs that are potent inhibitors for CYP2D6 or CYP3A4 may increase the AUC of galantamine. Multiple dose pharmacokinetic studies demonstrated that the AUC of galantamine increased 30% and 40%, respectively, during co-administration of ketoconazole and paroxetine. As co-administered with erythromycin, another CYP3A4 inhibitor, the galantamine AUC increased only 10%. Population PK analysis with a database of 852 patients with Alzheimer's disease showed that the clearance of galantamine was decreased about 25-33% by concurrent administration of amitriptyline (n = 17), fluoxetine (n = 48), fluvoxamine (n = 14), and quinidine (n = 7), known inhibitors of CYP2D6.

Concurrent administration of H_2-antagonists demonstrated that ranitidine did not affect the pharmacokinetics of galantamine, and cimetidine increased the galantamine AUC by approximately 16%.

(B) ***Effect of REMINYL® on the metabolism of other drugs:*** In vitro studies show that galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 and CYP2E1. This indicated that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low. Multiple doses of galantamine (24 mg/day) had no effect on the pharmacokinetics of digoxin and warfarin (R- and S-forms). Galantamine had no effect on the increased prothrombin time induced by warfarin.

CLINICAL TRIALS

The effectiveness of REMINYL® (galantamine hydobromide) as a treatment for Alzheimer's Disease is demonstrated by the results of 4 randomized, double-blind, placebo-controlled clinical investigations in patients with probable Alzheimer's Disease [diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination scores that were ≥ 10 and ≤ 24]. Doses studied were 8-32 mg/day given as twice daily doses. In 3 of the 4 studies patients were started on a low dose of 8 mg, then titrated weekly by 8 mg/day to 24 or 32 mg as assigned. In the fourth study (USA 4-week Dose-Escalation Fixed-Dose Study) dose escalation of 8 mg/day occurred over 4 week intervals. The mean age of patients participating in the 4 REMINYL® trials was 75 years with a range of 41 to 100. Approximately 62% of patients were women and 38% were men. The racial distribution was White 94%, Black 3% and other races 3%. Two other studies examined a three times daily dosing regimen; these also showed or suggested benefit but did not suggest an advantage over twice daily dosing.

Study Outcome Measures: In each study, the primary effectiveness of REMINYL® was evaluated using a dual outcome assessment strategy as measured by the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Impression of Change (CIBIC-plus).

The ability of REMINYL®to improve cognitive performance was assessed with the cognitive sub-scale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study had mean scores on ADAS-cog of approximately 27 units, with a range from 5 to 69. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's disease suggests that they gain 6 to 12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in REMINYL® trials was approximately 4.5 units per year.

The ability of REMINYL®to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-plus. The CIBIC-plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-plus reflect clinical experience from the trial or trials in which it was used and can not be compared directly with the results of CIBIC-plus evaluations from other clinical trials. The CIBIC-plus used in the trials was a semi-structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of 4 major areas of patient function: general, cognitive, behavioral and activities of daily living. It represents the assessment of a skilled clinician based on his/her observation at an interview with the patient, in combination with information supplied by a caregiver familiar with the behavior of the patient over the interval rated. The CIBIC-plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved", to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening". The CIBIC-plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

U.S. Twenty-One-Week Fixed-Dose Study

In a study of twenty-one weeks' duration, 978 patients were randomized to doses of 8, 16, or 24 mg of REMINYL® per day, or to placebo, each given in 2 divided doses. Treatment was initiated at 8 mg/day for all patients randomized to REMINYL®, and increased by 8 mg/day every 4 weeks. Therefore, the maximum titration phase was 8 weeks and the minimum maintenance phase was 13 weeks (in patients randomized to 24 mg/day of REMINYL®).

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all four dose groups over the 21 weeks of the study. At 21 weeks of treatment, the mean differences in the ADAS-cog change scores for the REMINYL®-treated patients compared to the patients on placebo were 1.7, 3.3, and 3.6 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo and to the 8 mg/day treatment. There was no statistically significant difference between the 16 mg/day and 24 mg/day dose groups.

Figure 1: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 21 Weeks (5 Months) of Treatment [1]

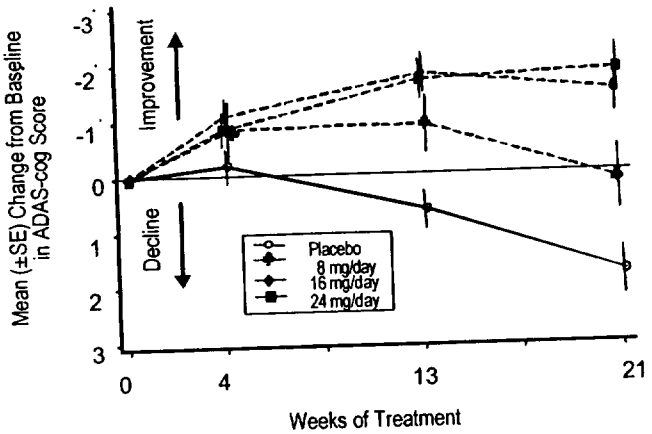
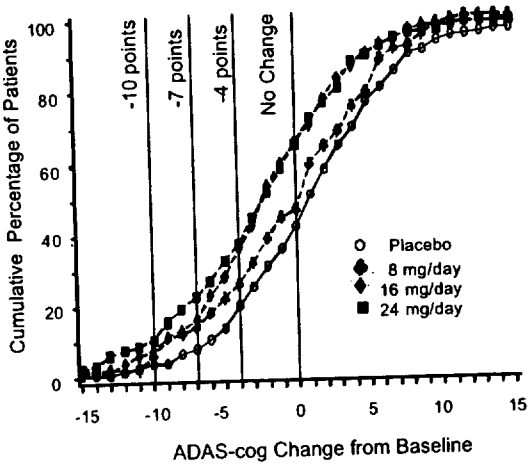


Figure 2 illustrates the cumulative percentages of patients from each of the four treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores (10 point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the REMINYL® groups are more likely to show the greater improvements.

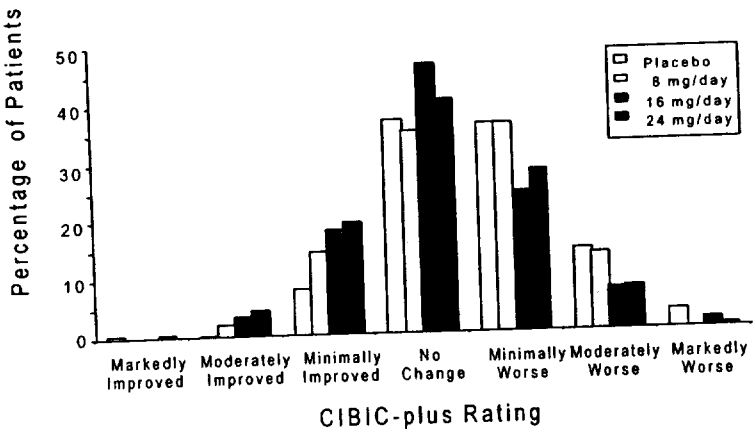
Figure 2: Cumulative Percentage of Patients Completing 21 Weeks of Double-blind Treatment with Specified Changes from Baseline in ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 84%, 8 mg/day 77%, 16 mg/day 78% and 24 mg/day 78%.



	Change in ADAS-cog			
Treatment	-10	-7	-4	0
Placebo	3.6%	7.6%	19.6%	41.8%
8 mg/day	5.9%	13.9%	25.7%	46.5%
16 mg/day	7.2%	15.9%	35.6%	65.4%
24 mg/day	10.4%	22.3%	37.0%	64.9%

Effects on the CIBIC-plus: Figure 3 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the four treatment groups who completed 21 weeks of treatment. The REMINYL®-placebo differences for these groups of patients in mean rating were 0.15, 0.41and 0.44 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo. The differences vs. the 8 mg/day treatment for the 16 and 24 mg/day treatments were 0.26 and 0.29, respectively. There were no statistically significant differences between the 16 mg/day and 24 mg/day dose groups.

Figure 3: Distribution of CIBIC-plus Ratings at Week 21



U.S. Twenty-Six-Week Fixed-Dose Study

In a study of 26 weeks' duration, 636 patients were randomized to either a dose of 24 mg or 32 mg of REMINYL® per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose titration phase and a 23-week maintenance phase.

Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the REMINYL®- treated patients compared to the patients on placebo were 3.9 and 3.8 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 4: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

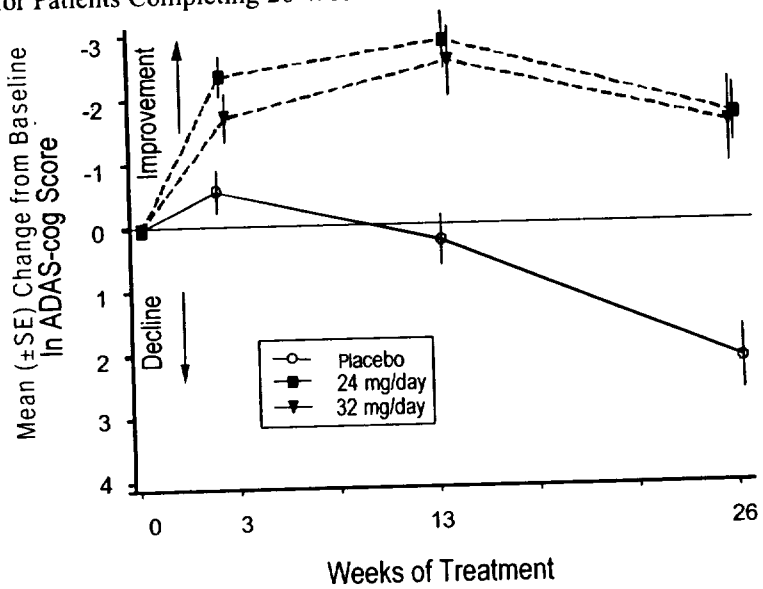
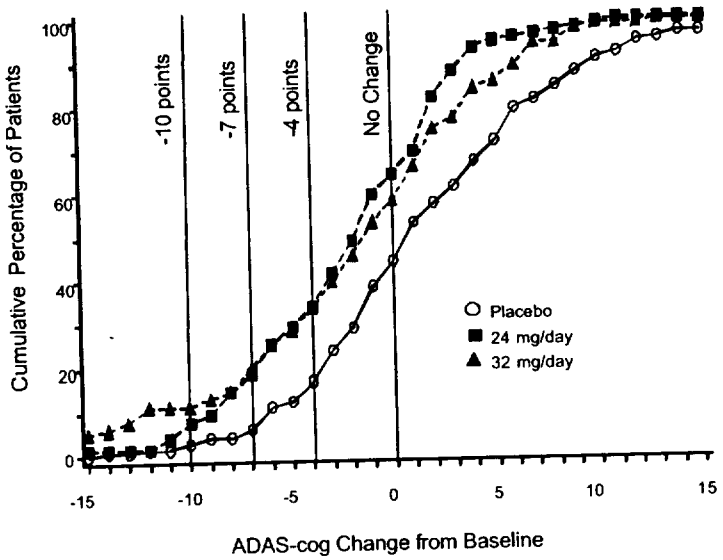


Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to REMINYL® and placebo have a wide range of responses, but that the REMINYL® groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

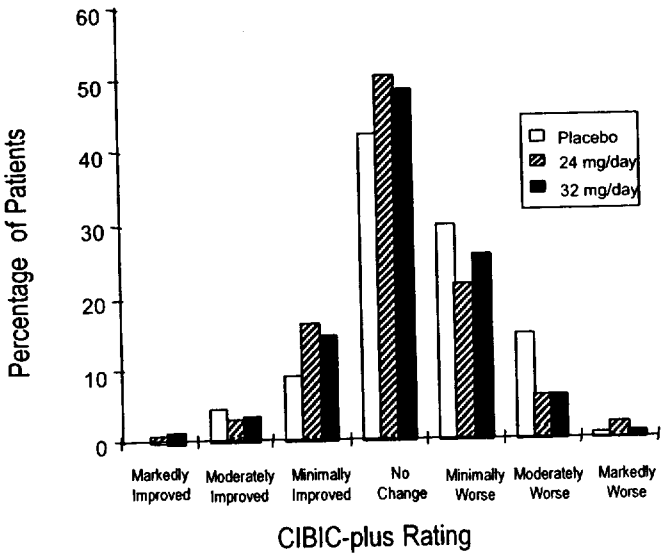
Figure 5: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline in ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 81%, 24 mg/day 68%, and 32 mg/day 58%.



	Change in ADAS-cog			
Treatment	-10	-7	-4	0
Placebo	2.1%	5.7%	16.6%	43.9%
24 mg/day	7.6%	18.3%	33.6%	64.1%
32 mg/day	11.1%	19.7%	33.3%	58.1%

Effects on the CIBIC-plus: Figure 6 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean REMINYL®-placebo differences for these groups of patients in the mean rating were 0.28 and 0.29 units for 24 and 32 mg/day of REMINYL®, respectively. The mean ratings for both groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 6: Distribution of CIBIC-plus Ratings Week 26



International Twenty-Six-Week Fixed-Dose Study

In a study of 26 weeks' duration identical in design to the USA Twenty-Six-Week Fixed-Dose Study, 653 patients were randomized to either a dose of 24 mg or 32 mg of REMINYL® per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose titration phase and a 23-week maintenance phase.

Effects on the ADAS-cog: Figure 7 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the REMINYL®-treated patients compared to the patients on placebo were 3.1 and 4.1 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 7: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

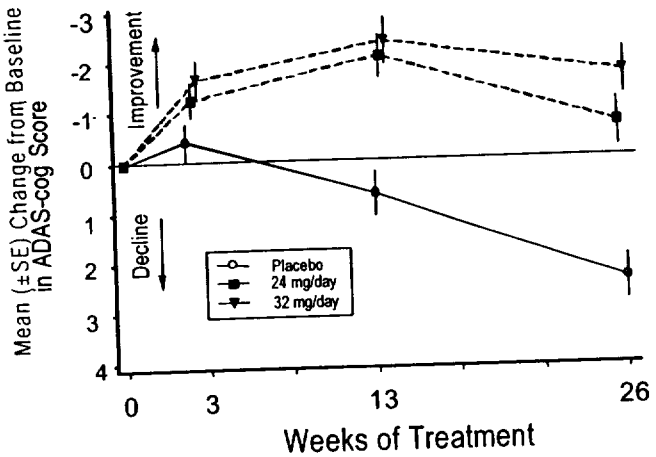
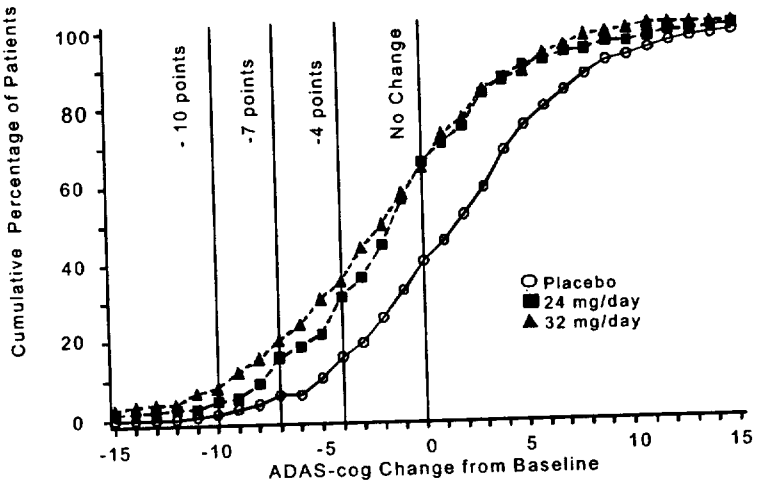


Figure 8 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to REMINYL® and placebo have a wide range of responses, but that the REMINYL® groups are more likely to show the greater improvements.

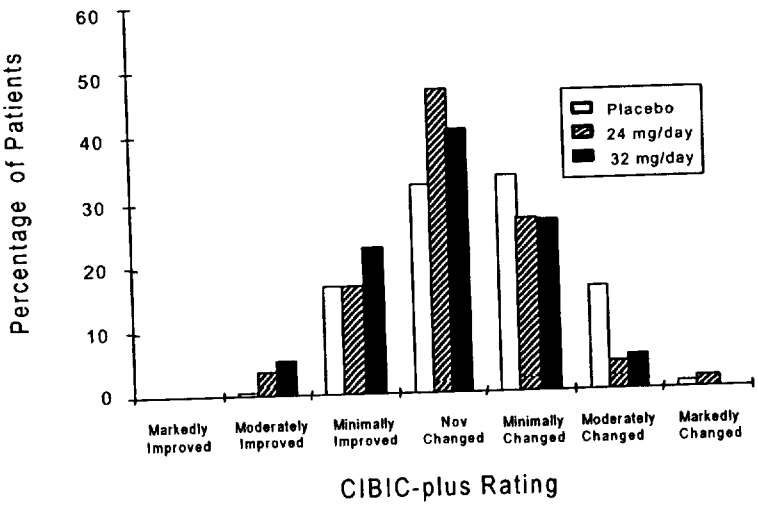
Figure 8: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline in ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 87%, 24 mg/day 80%, and 32 mg/day 75%.



	Change in ADAS-cog			
Treatment	-10	-7	-4	0
Placebo	1.2%	5.8%	15.2%	39.8%
24 mg/day	4.5%	15.4%	30.8%	65.4%
32 mg/day	7.9%	19.7%	34.9%	63.8%

Effects on the CIBIC-plus: Figure 9 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean REMINYL®-placebo differences for these groups of patients in the mean rating of change from baseline were 0.34 and 0.47 for 24 and 32 mg/day of REMINYL®, respectively. The mean ratings for the REMINYL® groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 9: Distribution of CIBIC-plus Rating at Week 26



International Thirteen-Week Flexible-Dose Study

In a study of 13 weeks' duration, 386 patients were randomized to either a flexible dose of 24-32 mg/day of REMINYL® or to placebo, each given in two divided doses. The 13-week study was divided into a 3-week dose titration phase and a 10-week maintenance phase. The patients in the active treatment arm of the study were maintained at either 24 mg/day or 32 mg/day at the discretion of the investigator.

Effects on the ADAS-cog: Figure 10 illustrates the time course for the change from baseline in ADAS-cog scores for both dose groups over the 13 weeks of the study. At 13 weeks of treatment, the mean difference in the ADAS-cog change score for the treated patients compared to the patients on placebo was –1.9. REMINYL® at a dose of 24-32 mg/day was statistically significantly superior to placebo.

Figure 10: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 13 Weeks of Treatment

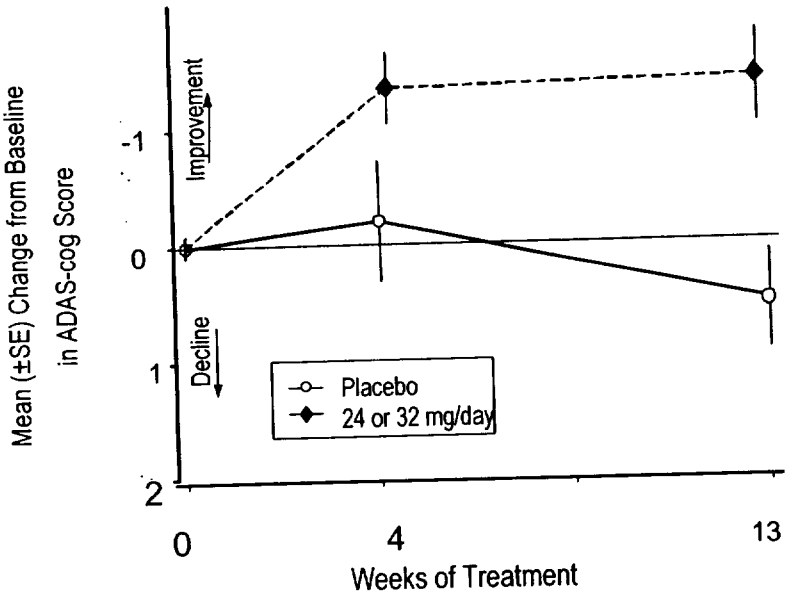
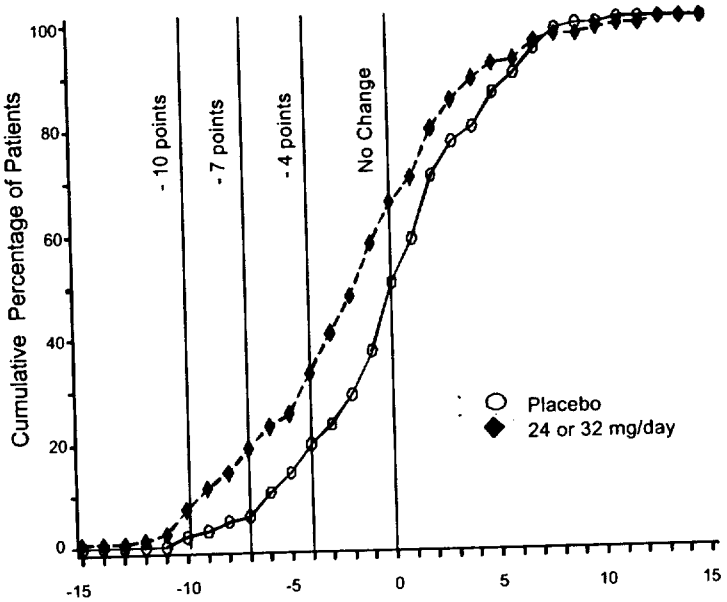


Figure 11 illustrates the cumulative percentages of patients from each of the two treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to REMINYL® and placebo have a wide range of responses, but that the REMINYL® group is more likely to show the greater improvement.

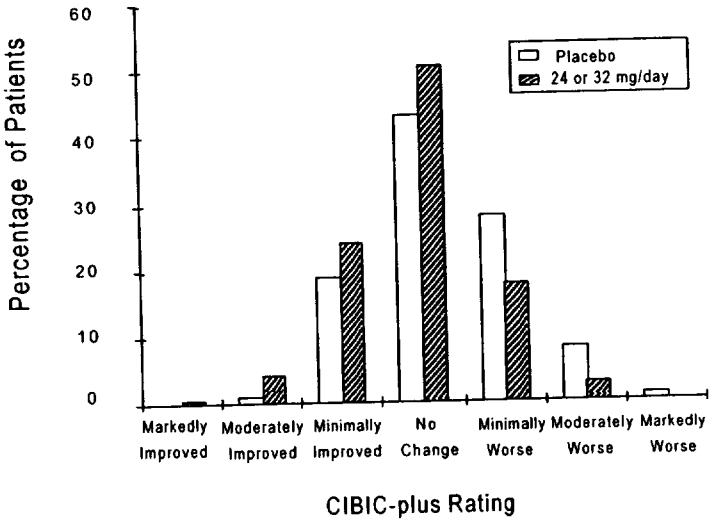
Figure 11: Cumulative Percentage of Patients Completing 12 Weeks of Double-blind Treatment with Specified Changes from Baseline in ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 90%, 24-32 mg/day 67%.



	Change in ADAS-cog			
Treatment	-10	-7	-4	0
Placebo	1.9%	5.6%	19.4%	50.1%
24 or 32 mg/day	7.1%	18.8%	32.9%	65.3%

Effects on the CIBIC-plus: Figure 12 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the two treatment groups who completed 12 weeks of treatment. The mean REMINYL®-placebo differences for the group of patients in the mean rating of change from baseline was 0.37 units. The mean rating for the 24-32-mg/day group was statistically significantly superior to placebo.

Figure 12: Distribution of CIBIC-plus Ratings at Week 12



Age, gender and race: Patient's age, gender, or race did not predict clinical outcome of treatment.

INDICATIONS AND USAGE

Reminyl ® (galantamine hydrobromide) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS

REMINYL ® is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulation.

WARNINGS

Anesthesia

Galantamine, as a cholinesterase inhibitor, is likely to exaggerate the neuromuscular blockade effects of succinylcholine-type and similar neuromuscular blocking agents during anesthesia.

Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and AV block. These actions may be particularly important to patients with supraventricular cardiac conduction disorders or to patients taking other drugs concomitantly that significantly slow heart rate. Postmarketing surveillance of marketed anticholinesterase inhibitors has shown, however, that, bradycardia and all types of heart block have been reported in patients both with and without known underlying cardiac conduction

abnormalities. Therefore all patients should be considered at risk for adverse effects on cardiac conduction.

In randomized controlled trials, bradycardia was reported more frequently in galantamine-treated patients than in placebo-treated patients, but rarely led to treatment discontinuation. The overall frequency of this event was 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo. No increased incidence of heart block was observed at the recommended doses.

Patients treated with galantamine up to 24 mg/day using the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo 0.7% [2/286]; 4 mg BID 0.4% [3/692]; 8 mg BID 1.3% [7/552]; 12 mg BID 2.2% [6/273]).

Gastrointestinal Conditions
Through their primary action, cholinomimetics may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g., those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of REMINYL® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

REMINYL®, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting, diarrhea, anorexia, and weight loss. (see **ADVERSE REACTIONS**)

Genitourinary
Although this was not observed in clinical trials with REMINYL®, cholinomimetics may cause bladder outflow obstruction.

Neurological Conditions
Seizures: Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's Disease. In clinical trials, there was no increase in the incidence of convulsions with REMINYL® compared to placebo.

Pulmonary Conditions
Because of its cholinomimetic action, galantamine should be prescribed with care to patients with a history of severe asthma or obstructive pulmonary disease.

PRECAUTIONS

Information for Patients and Caregivers: Caregivers should be instructed in the recommended administration (twice per day, preferably with morning and evening meal) and dose escalation (dose increases should follow minimum of four weeks at prior dose).

Patients and caregivers should be advised that the most frequent adverse events associated with use of the drug can be minimized by following the recommended dosage and administration.

Patients and caregivers should be informed that if therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Special Populations

Hepatic Impairment
In patients with moderately impaired hepatic function, dose titration should proceed cautiously (see **CLINICAL PHARMACOLOGY and DOSAGE and ADMINISTRATION**). The use of REMINYL® in patients with severe hepatic impairment is not recommended.

Renal Impairment
In patients with moderately impaired renal function, dose titration should proceed cautiously (see **CLINICAL PHARMACOLOGY and DOSAGE and ADMINISTRATION**). In patients with severely impaired renal function (CL_{cr} < 9 mL/min.) the use of REMINYL® is not recommended.

Drug-Drug Interactions

Use With Anticholinergics
REMINYL ® (galantamine hydrobromide) has the potential to interfere with the activity of anticholinergic medications.

Use With Cholinomimetics And Other Cholinesterase Inhibitors
A synergistic effect is expected when cholinesterase inhibitors are given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

A) Effect of Other Drugs on Galantamine

In Vitro
CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide; CYP2D6 leads to the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged, no single pathway appears predominant.

In Vivo

Cimetidine and Ranitidine: Galantamine was administered as a single dose of 4 mg on day 2 of a 3-day treatment with either cimetidine (800 mg daily) or ranitidine (300 mg daily). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the PK of galantamine

Ketoconazole: Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg bid for 4 days, increased the AUC of galantamine by 30 %.

Erythromycin: Erythromycin, a moderate inhibitor of CYP3A4, at a dose of 500mg qid for 4 days affected the AUC of galantamine minimally (10% increase).

Paroxetine: Paroxetine, a strong inhibitor of CYP2D6, at 20 mg per day for 16 days increased the oral bioavailibility of galantamine by about 40 %.

B) **Effect of Galantamine on Other Drugs**

In vitro
Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low.

In vivo
Warfarin: Galantamine at 24 mg/day had no effect on the pharmacokinetics of R-and-S-warfarin (25 mg single dose) or on the prothrombin time. The protein binding of warfarin was unaffected by galantamine.

Digoxin: Galantamine at 24 mg/day had no effect on the steady-state pharmacokinetics of digoxin (0.375 once daily) when they were coadministered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia.

Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 24-month oral carcinogenicity study in rats, a slight increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m^2 basis or 6 times on an exposure [AUC] basis and 30 mg/kg/day (12 times MRHD on a mg/m^2 basis or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m^2 and AUC basis).

Galantamine was not carcinogenic in a 6 month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24 month oral carcinogenicty study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m^2 basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames *S. typhimurium* or *E. coli* reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m^2 basis) for 14 days prior to mating in females and for 60 days prior to mating in males.

Pregnancy

Pregnancy Category B: In a study in which rats were dosed from day 14 (females) or day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the Maximum Recommended Human Dose [MRHD] on a mg/m^2 basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m^2 basis) during the period of organogenesis.

There are no adequate and well-controlled studies of REMINYL® in pregnant women. REMINYL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether galantamine is excreted in human breast milk. REMINYL® has no indication for use in nursing mothers.

Pediatric Use
There are no adequate and well-controlled trials documenting the safety and efficacy of galantamine in any illness occurring in children. Therefore, use of REMINYL® in children is not recommended.

ADVERSE REACTIONS
Adverse Events Leading to Discontinuation: In two large scale, placebo-controlled trials of 6 months duration, in which patients were titrated weekly from 8 to 16 to 24, and to 32 mg/day, the risk of discontinuation because of an adverse event in the galantamine group exceeded that in the placebo group by about threefold. In contrast, in a 5-month trial with escalation of the dose by 8mg/day every 4 weeks, the overall risk of discontinuation because of an adverse event was 7%, 7%, and 10% for the placebo, galantamine 16 mg/day, and galantamine 24 mg/day groups, respectively, with gastrointestinal adverse effects the principal reason for discontinuing galantamine. Table 1 shows the most frequent adverse events leading to discontinuation in this study.

Table 1: Most Frequent Adverse Events Leading to Discontinuation in a Placebo-controlled, Double-blind Trial with a 4 Week Dose-Escalation Schedule

	4-week Escalation		
Adverse Event	Placebo N=286	16 mg/day N=279	24 mg/day N=273
Nausea	<1%	2%	4%
Vomiting	0%	1%	3%
Anorexia	<1%	1%	<1%
Dizziness	<1%	2%	1%
Syncope	0%	0%	1%

Adverse Events Reported in Controlled Trials: The reported adverse events in REMINYL® trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ.

The majority of these adverse events occurred during the dose-escalation period. In those patients who experienced the most frequent adverse event, nausea, the median duration of the nausea was 5-7 days.

Administration of REMINYL® with food, the use of anti-emetic medication, and ensuring adequate fluid intake may reduce the impact of these events.

The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate on placebo with the recommended maintenance dose of either 16 or 24 mg/day of REMINYL® under conditions of every 4 week dose escalation for each dose increment of 8 mg/day, are shown in Table 2. These events were primarily gastrointestinal and tended to be less frequent with the16 mg/day recommended initial maintenance dose.

Table 2: The Most Frequent Adverse Events in the Placebo-controlled Trial with Dose Escalation every 4 weeks occurring in at least 5% of Patients Receiving REMINYL® and at least twice the rate on Placebo.

	Placebo	REMINYL® 16 mg/day	REMINYL® 24 mg/day
Adverse Event	N=286	N=279	N=273
Nausea	5%	13%	17%
Vomiting	1%	6%	10%
Diarrhea	6%	12%	6%
Anorexia	3%	7%	9%
Weight decrease	1%	5%	5%

Table 3: The most common adverse events (adverse events occurring with an incidence of at least 2% with REMINYL® treatment and in which the incidence was greater than with placebo treatment) are listed in Table 3 for four placebo-controlled trials for patients treated with 16 or 24 mg/day of REMINYL®.

Table 3: Adverse Events Reported in at least 2% of Patients with Alzheimer's Disease Administered REMINYL® and at a Frequency Greater than with Placebo

Body System Adverse Event	Placebo (N=801)	REMINYL® [a] (N=1040)
Body as a whole - general disorders		
Fatigue	3%	5%
Syncope	1%	2%
Central & peripheral nervous system disorders		
Dizziness	6%	9%
Headache	5%	8%
Tremor	2%	3%
Gastro-intestinal system disorders		
Nausea	9%	24%
Vomiting	4%	13%
Diarrhea	7%	9%
Abdominal pain	4%	5%
Dyspepsia	2%	5%
Heart rate and rhythm disorders		
Bradycardia	1%	2%
Metabolic and nutritional disorders		
Weight decrease	2%	7%
Psychiatric disorders		
Anorexia	3%	9%
Depression	5%	7%
Insomnia	4%	5%
Somnolence	3%	4%
Red blood cell disorders		
Anemia	2%	3%
Respiratory system disorders		
Rhinitis	3%	4%
Urinary system disorders		
Urinary tract infection	7%	8%
Hematuria	2%	3%

a: Adverse events in patients treated with 16 or 24 mg/day of REMINYL® in four placebo-controlled trials are included

Adverse events occurring with an incidence of at least 2% in placebo-treated patients that was either equal to or greater than with REMINYL® treatment were constipation, agitation, confusion, anxiety, hallucination, injury, back pain, peripheral edema, asthenia, chest pain, urinary incontinence, upper respiratory tract infection, bronchitis, coughing, hypertension, fall, and purpura.

There were no important differences in adverse event rate related to dose or sex. There were too few non-Caucasian patients to assess the effects of race on adverse event rates.

No clinically relevant abnormalities in laboratory values were observed.

Other Adverse Events Observed During Clinical Trials

REMINYL® was administered to 3055 patients with Alzheimer's Disease. A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's Disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1000 patients received galantamine for at least one year and approximately 200 patients received galantamine for two years.

To establish the rate of adverse events, data from all patients receiving any dose of galantamine in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All adverse events occurring in approximately 0.1% are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients; rare adverse events- those occurring in fewer than 1/1000 patients. These adverse events are not necessarily related to REMINYL® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body As a Whole – General Disorders: *Frequent:* chest pain

Cardiovascular System Disorders: *Infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure

Central & Peripheral Nervous System Disorders: *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia

Gastrointestinal System Disorders: *Frequent:* flatulence; *Infrequent:* gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *rare:* esophageal perforation

Heart Rate & Rhythm Disorders: *Infrequent:* AV block, palpitation, atrial fibrillation, QT prolonged, bundle branch block, supraventricular tachycardia, T wave inversion, ventricular tachycardia

Metabolic & Nutritional Disorders: *Infrequent:* hyperglycemia, alkaline phosphatase increased

Platelet, Bleeding & Clotting Disorders: *Infrequent:* purpura, epistaxis, thrombocytopenia

Psychiatric Disorders: *Infrequent:* apathy, paroniria, paranoid reaction, libido increased, delirium

Urinary System Disorders: *Frequent:* incontinence; *Infrequent:* hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug.

As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or fasciculations, some or all of the following signs of cholinergic crisis may develop: severe nausea, vomiting, gastrointestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Tertiary anticholinergics such as atropine may be used as an antidote for REMINYL® overdosage. Intravenous atropine sulphate titrated to effect is recommended at an initial dose of 0.5 to 1.0 mg i.v. with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics. It is not known whether REMINYL® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included hypoactivity, tremors, clonic convulsions, salivation, lacrimation, chromodacryorrhea, mucoid feces, and dyspnea.

DOSAGE AND ADMINISTRATION

The dosage of REMINYL® shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16–24 mg/day given in a BID regimen. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of REMINYL® might provide additional benefit for some patients.

The recommended starting dose of REMINYL® is 4 mg twice a day (8 mg/day). After a minimum of 4 weeks of treatment, if this dose is well tolerated, the dose should be increased to 8 mg twice a day (16 mg/day). A further increase to 12 mg twice a day (24 mg/day) should be attempted only after a minimum of 4 weeks at the previous dose.

REMINYL® should be administered twice a day, preferably with morning and evening meals.

Patients and caregivers should be informed that if therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

The abrupt withdrawal of REMINYL® in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of REMINYL® are lost, however, when the drug is discontinued.

Doses in Special Populations

Galantamine plasma concentrations may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), the dose should generally not exceed 16 mg/day. The use of REMINYL® in patients with severe hepatic impairment (Child-Pugh score of 10-15) is not recommended.

For patients with moderate renal impairment the dose should generally not exceed 16 mg/day. In patients with severe renal impairment (creatinine clearance <9 ml/min), the use of REMINYL® is not recommended.

HOW SUPPLIED

REMINYL® (galantamine hydrobromide) tablets are imprinted "JANSSEN" on one side, and "G" and the strength "4", "8", or "12" on the other.

4 mg off-white tablet: bottles of 60 NDC 50458-390-60

8 mg pink, scored tablet: bottles of 60 NDC 50458-391-60

12 mg orange-brown tablet: bottles of 60 NDC 50458-392-60

Storage and Handling
REMINYL® tablets should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

US Patent No. 4,663,318

Manufactured by:
Janssen-Cilag SpA
Latina, Italy

Distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

Diltiazem (Z)

Cardiovascular AEs

The sponsor found no notable differences in risk for cardiovascular AEs for the Z+G group compared to the G group but the data suggested increased risk for falls in the Z+G group. The risk for falls was 11.9% (8/67) in the Z+G group compared to 5.3% (79/1486) in the G group, 3.8% (1/26) in the Z alone group, and 5.4% (37/688) in the N group.

Heart Rate, PR Interval

There did not appear to be evidence of increased risk for notable decreases in heart rate or prolongation of PR interval for Z+G compared to the G group based on the mean change from baseline data. In study USA-10, the mean change from baseline for heart rate using pulse was –2.4 bpm for the V+G group compared to –2.2 bpm for the G group, 1.1 bpm for the Z alone group and –1.0 bpm for the N group. The mean change from baseline for heart rate using ECG was –4.9 bpm for the V+G group compared to –2.7 bpm for the G group, 12.1 bpm for the V alone group and –1.4 bpm for the N group. The PR interval mean change from baseline was –0.1 msec for the V+G group compared to 3.3msec for the G group, -7.6 msec for the V alone group and 2.3 msec for the N group.

Combined Medications Group (CM)

Cardiovascular AEs

The group treated with galantamine plus one or more of the medications identified above (combined medications group) had an increased risk for bradycardia and falls compared to the group treated with galantamine alone. In the group treated with G+CM, the risk for bradycardia was 5.3% (20/380) compared to 1.7% (20/1173) in the G group, 2% (3/150) in the CM group, and 0.4% (2/564) in the N group. In the G+CM group, the risk for fall was 7.6% (29/380) compared to 4.9% (50/1173) in the G group, 6% (9/150) in the CM group, and 5.1% (29/564) in the N group.

Heart Rate, PR Interval

There did not appear to be evidence of increased risk for notable decreases in heart rate or prolongation of PR interval for the group treated with G+CM group compared to the G group based on the mean change from baseline data. The mean change from baseline for heart rate using pulse was –1.5 bpm for the G+CM group compared to –2.5 bpm for the G group, -0.1 bpm for the CM group and –1.2 bpm for the N group. The mean change from baseline for heart rate using ECG was –2.9 bpm the G+CM group compared to –2.8 bpm for the G group, 0.8 bpm for the CM group and –1.5 bpm for the N group. The PR interval mean change from baseline was –0.9 msec for the G+CM group compared to 4.5 msec for the G group, -2.4 msec for the CM group and 3.2 msec for the N group.

Discussion

The results of the requested analyses suggest that risks for some cardiovascular and related AEs were increased in individuals taking galantamine PLUS medications that affect heart rate and cardiac conduction compared to those taking galantamine alone.

Concomitant use of galantamine with a medication effecting heart rate and cardiac conduction did not appear to result in substantially greater mean decreases in heart rate or mean increases in PR interval when compared to galantamine alone. The findings from these analyses may initially appear reassuring since the cardiovascular AE risks were only mildly elevated when galantamine was used in combination with a medication that affects heart rate and cardiac conduction. In interpreting these results one must remember that the population treated in a development program is highly selected and less heterogeneous than the population that will be exposed once a drug is marketed. Therefore, despite observing fairly small increases in risk for certain cardiovascular events when galantamine was used in combination with medications that affect heart rate and cardiac conduction, we cannot be certain that these findings will generalize to a more heterogeneous population with a higher prevalence of underlying comorbidities. Labeling should reflect the potential for increased risk of bradycardia and falls when galantamine is used in combination with other medications that affect heart rate and cardiac conduction.

Table 2. A summary of pulse*, heart rate#, and PR-interval mean changes from baseline from study USA-10, by drug usage

Drug	Galantamine	Digoxin+Galantamine	Digoxin	Neither
N	649	43	15	271
Pulse bpm	-2.4	0.1	-0.7	-0.9
Heart Rate /min	-2.8	-3.0	-2.3	-0.9
PR interval msec	3.1	2.6	-0.8	2.1
Drug	Galantamine	β-blocker+Galantamine	β-blocker	Neither
N	583	109	43	243
Pulse bpm	-2.4	-1.3	0.1	-1.1
Heart Rate /min	-3.1	-1.7	-2.2	-0.8
PR Interval msec	3.6	0.2	-2.2	2.7
Drug	Galantamine	Verapamil+Galantamine	Verapamil	Neither
N	669	23	7	279
Pulse bpm	-2.2	-2.9	-1.0	-0.9
Heart Rate/min	-2.8	-5.4	1.6	-0.8
PR Interval msec	3.3	-5.0	1.6	2.0
Drug	Galantamine	Diltiazem+Galantamine	Diltiazem	Neither
N	651	41	13	273
Pulse bpm	-2.2	-2.4	1.1	-1.0
Heart rate/min	-2.7	-4.9	12.1	-1.4
PR Interval msec	3.3	-0.1	-7.5	2.3
Drug	Galantamine	Combined+Galantamine	Combined	Neither
N	500	192	72	214
Pulse bpm	-2.5	-1.5	-0.1	-1.2
Heart Rate/min	-2.8	-2.9	0.8	-1.5
PR Interval	4.5	-0.9	-2.4	3.2

*pulse data taken from vital signs recordings
#heart rate data taken from ECG recordings

Table 3. A summary selected adverse events occurring in more than 1% of subjects in any of the drug groups, studies INT-1, USA-1, and USA-10

	Digoxin 33	Digoxin+Galantamine 78	Galantamine 1475	Neither 681
Bradycardia	0	2.6% (2)	2.6% (38)	0.7% (5)
Syncope	0	1.3% (1)	2.4% (35)	0.9% (6)
Fall	3% (1)	6.4% (5)	5.6% (82)	5.4% (37)
Hypertension	6.1% (2)	0	3.8% (56)	3.5% (24)
Oedema dependent	0	1.3% (1)	1.3% (19)	1.8% (12)
Heart murmur	6.1% (2)	3.8% (3)	1% (15)	0.7% (5)
Cardiac Failure	9.1% (3)	3.8% (3)	0.4% (6)	0.6% (4)
Hypotension	3% (1)	1.3% (1)	0.5% (8)	0.4% (3)
ECG Abnormal	3% (1)	1.3% (1)	0.4% (6)	0.6% (4)
Cardiomegaly	0	1.3% (1)	0.1% (1)	0
Extrasystoles	0	0	1.3% (19)	0.6% (4)
Atrial Fibrillation	6.1% (2)	2.6% (2)	0.6% (9)	0.6% (4)
Tachycardia	6.1% (2)	0	0.5% (8)	0.6% (4)
Arrhythmia ventricular	3% (1)	0	0.3% (4)	0.4% (3)
T wave inversion	3% (1)	0	0.2% (3)	0.1% (1)
SVT	0	2.6% (2)	0.1% (2)	0.1% (1)
Drug	β-blocker 92	β-blocker+Galantamine 231	Galantamine 1322	Neither 622
Bradycardia	2.2% (2)	6.9% (16)	1.8% (24)	0.5% (3)
Syncope	1.1% (1)	2.6% (6)	2.3% (30)	0.8% (5)
Fall	7.6% (7)	6.9% (16)	5.4% (71)	5% (31)
Hypertension	8.7% (8)	3.9% (9)	3.6% (47)	2.9% (18)
Oedema dependent	3.3% (3)	2.2% (5)	1.1% (15)	1.4% (9)
Heart murmur	2.2% (2)	0.9% (2)	1.2% (16)	0.8% (5)
Cardiac Failure	2.2% (2)	0.4% (1)	0.6% (8)	0.8% (5)
Hypotension	0	1.3% (3)	0.5% (6)	0.6% (4)
Hypotension postural	1.1% (1)	0	0.5% (6)	0.6% (4)
Hypertension aggravated	2.2% (2)	0.4% (1)	0	0.2% (1)
Extrasystoles	1.1% (1)	0.4% (1)	1.4% (18)	0.5% (3)
Atrial Fibrillation	1.1% (1)	0.4% (1)	0.6% (8)	0.8% (5)
Bundle Branch Block	1.1% (1)	1.3% (3)	0.6% (8)	0.6% (4)
AV block	0	1.3% (3)	0.5% (7)	0.3% (2)
Arrhythmia	2.2% (2)	0	0.5% (6)	0
Arrhythmia ventricular	1.1% (1)	0	0.3% (4)	0.5% (3)
Drug	Verapamil 21	Verapamil+Galantamine 49	Galantamine 1504	Neither 693
Bradycardia	4.8% (1)	4.1% (2)	2.5% (38)	0.6% (4)
Syncope	0	8.2% (4)	2.1% (32)	0.9% (6)
Fall	9.5% (2)	10.2% (5)	5.5% (82)	5.2% (36)
Hypertension	9.5% (2)	6.1% (3)	3.5% (53)	3.5% (24)
Oedema dependent	4.8% (1)	0	1.3% (20)	1.6% (11)
Heart murmur	0	0	1.2% (18)	1% (7)
Cardiac failure	0	4.1% (2)	0.5% (7)	1% (7)
Hypotension	4.8% (1)	2% (1)	0.5% (8)	0.4% (3)
Hypotension postural	0	2% (1)	0.3% (5)	0.7% (5)
Hypertension aggravated	4.8% (1)	0	0.1% (1)	0.7% (5)
Extrasystoles	0	0	1.3% (19)	0.6% (4)
Atrial fibrillation	0	2% (1)	0.7% (10)	0.9% (6)
Bundle branch clock	0	2% (1)	0.7% (10)	0.7% (5)
Arrhythmia	4.8% (1)	2% (1)	0.5% (7)	0.1% (1)
Drug	Diltiazem 26	Diltiazem+Galantamine 107	Galantamine 1486	Neither 688
Bradycardia	0	3% (2)	2.6% (38)	0.7% (5)
Syncope	0	1.5% (1)	2.4% (35)	0.9% (6)
Falls	3.8% (1)	11.9% (8)	5.3% (79)	5.4% (37)
Hypertension	3.8% (1)	4.5% (3)	3.6% (53)	3.6% (25)
Oedema dependent	0	1.5% (1)	1.3% (19)	1.7% (12)

Heart murmur	0	3% (2)	1.1% (16)	1% (7)
Cardiac failure	0	1.5% (1)	0.5% (8)	1% (7)
Cyanosis	0	1.5% (1)	0	0
Extrasystoles	0	0	1.3% (19)	0.6% (4)
Atrial fibrillation	0	4.5% (3)	0.5% (8)	0.9% (6)
Bundle branch block	0	1.5% (1)	0.7% (10)	0.7% (5)
Palpitation	0	1.5% (1)	0.5% (7)	0.3% (2)
Arrhythmia ventricular	0	1.5% (1)	0.2% (3)	0.6% (4)
SVT	7.7% (2)	3% (2)	0.1% (1)	0
	Combined 150	Combined Galantamine 1080	Galantamine 1173	Neither 564
Bradycardia	2% (3)	5.3% (20)	1.7% (20)	0.4% (2)
Syncope	0.7% (1)	2.9% (11)	2.1% (25)	0.9% (5)
Falls	6% (9)	7.6% (29)	4.9% (58)	5.1% (29)
Hypertension	7.3% (11)	3.9% (15)	3.5% (41)	2.7% (15)
Oedema dependent	2.7% (4)	1.8% (7)	1.1% (13)	1.4% (8)
Heart murmur	2.7% (4)	1.3% (5)	1.1% (13)	0.5% (3)
Cardiac failure	2.7% (4)	1.1% (4)	0.4% (5)	0.5% (3)
Hypotension	1.3% (2)	1.1% (4)	0.4% (5)	0.4% (2)
Hypertension aggravated	1.3% (2)	0.3% (1)	0	0.4% (2)
Extrasystoles	0.7% (1)	0.3% (1)	1.5% (18)	0.5% (3)
Atrial fibrillation	1.3% (2)	1.6% (6)	0.4% (5)	0.7% (4)
Bundle branch block	0.7% (1)	1.1% (4)	0.6% (7)	0.7% (4)
Tachycardia	1.3% (2)	0.3% (1)	0.6% (7)	0.7% (4)
Arrhythmia	1.3% (2)	0.5% (2)	0.5% (6)	0
Arrhythmia ventricular	1.3% (2)	0.3% (1)	0.3% (3)	0.4% (2)
SVT	1.3% (2)	0.5% (2)	0.1% (1)	0

Question 9

There were several individual patients mentioned in the NDA who suffered AEs, but for whom pertinent information about the AE was not available in the NDA submission or the amendment to the NDA. Please review your records for the pertinent information on the following patients:

In GAL-FRA-1, the study report described one subject with a clinically significant decrease in platelet count at the post-study visit. What were the baseline and end-of-study platelet counts?

The sponsor explained that the patient with the decline in platelet count was a 44 year old female with chronic renal insufficiency who had a screening platelet count of 154 giga/L (normal range 150-500) and a count of 139 giga/L at the final visit (day 3). No other platelet counts were available.

Patient INT-3/A03057 developed jaundice and was removed from the trial for this reason. Please provide the patient's total bilirubin, AST, ALT, and alkaline phosphatase values at baseline and at the time of discontinuation (and any that were measured in between). What kind of work-up did the patient have for the jaundice and what was the outcome?

The sponsor responded that after completing trial INT-1 where this subject received galantamine 12mg bid, she entered an extension (INT-3) and 3 days later fell and

fractured her hip and underwent surgical repair. She had normal LFTs 3 days prior to the fall. While hospitalized, she had elevated LFTs but the sponsor was not sure of the relationship of these results to her surgery. Her highest AST was 85U/L, ALT was 62U/L and total bilirubin was 2.5g/dL (42µmol/L). Less than 1 month later her ALT was 19U/L and total bilirubin was 1.1mg/dL (18µmol/L). The sponsor provided no diagnostic test results for this event and commented that anesthetic agent during surgery or another concomitant medication (valproate) may have contributed to the abnormal test result.

Patient 95-05X/B0406 was reported to have the AE "hepatic failure", yet it was evaluated as mild and non-serious. What were the patient's LFT values that led to the reporting of this AE?

The sponsor responded that this subject received placebo in trial 95-05 and then entered the open label extension. The patient received galantamine for the first month of the extension (reason for stopping not given). The ALT was elevated at baseline (47U/L) and the highest observed ALT was 57U/L. The patient had one abnormal AST (40U/L) and her total bilirubin was never>1mg/dL. The sponsor stated that the findings were not consistent with liver failure but did not explain why the investigator provided this diagnosis.

Patient USA-6/A50135 was an 84 year old female who received galantamine hydrobromide during an RCT and continued on galantamine during this extension trial. She developed pancreatitis and was hospitalized. No other details from the hospitalization were available. Please examine your records for information about the patient's pancreatitis including amylase and lipase values, abdominal CT scan findings, and any other pertinent tests. What was the outcome?

The sponsor responded that that during the preceding controlled trial this subject received galantamine and was hospitalized for nausea and that immediately prior to developing nausea she had been treated with Biaxin. A CT at this time revealed a normal pancreas but no amylase or lipase values were noted. Sixty nine days after entering open label treatment, the patient was hospitalized for pancreatitis. The sponsor noted that the subject was receiving 3 medications associated with pancreatitis (furosemide, sertraline, and ranitidine). The sponsor stated that amylase, lipase and CT results from this hospitalization were not available. The sponsor noted that the risk for pancreatitis in the controlled trials was the same for the galantamine and placebo groups and that the risk in the open label trials was comparable to risks described by National Hospital Discharge Survey data (1993).

Patient USA-10/A73226 developed early renal failure during the trial and was discontinued for this reason. Please provide the patient's BUN and creatinine at baseline and at the time of discontinuation (and any other measurements between those times). What was the outcome?

The sponsor noted that the subject had developed moderate pedal edema that was treated with a diuretic. One and a half months later the patient was hospitalized for refusal to eat and decreased activity. During the hospitalization the subject had early renal failure and was treated for dehydration. The sponsor provided lab results that demonstrated the subject had a baseline creatinine of 0.7mg/dL and developed a creatinine of 2.7mg/dL at the time of hospitalization along with a BUN of 99mg/dL, consistent with a pre-renal azotemia. The sponsor documented that on follow up, the subject's creatinine was 1mg/dL and the BUN was 19mg/dL.

Patients USA-10/A73639 and USA-3/A50173 both developed substantial falls in hemoglobin during their respective trials. In each of these patients' narratives, no information was provided concerning the patient's work-up for the cause of the anemia. Please provide any available information to explain the source of these two patients' anemia.

The sponsor documented that patient USA-10/A73639 had a colonoscopy that documented an ileocecal adenocarcinoma that likely caused the subject's anemia.

The sponsor noted that subject A50173 had a slight decline in Hgb from screening (13.3g/dL) to baseline (12.1g/dL) prior to receiving galantamine in the controlled trial. This subject's lowest Hgb was recorded during the open label extension (7.2g/dL). The sponsor stated that the subject discontinued for withdrawn consent approximately 1 month after the low value and at that time the Hgb was 9.2g/dL. The sponsor also commented that there was no available record of the results of any investigations for the cause of anemia.

Discussion- Question 9

The sponsor attempted to provide the requested additional information for subjects with laboratory abnormalities, although they did not have complete information for several of the identified subjects. The information provided by the sponsor does not alter the current understanding of galantamine's safety profile.

/S/ 1/25/01

Judith A. Racoosin, MD, MPH
Safety Team Leader

Review and Evaluation of Clinical Data
CLINICAL EFFICACY REVIEW OF NEW DRUG APPLICATION

NDA	**21169**
Sponsor:	**Janssen**
Drug:	**Galantamine**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Resubmission**
Correspondence Date:	**8/31/00**
Date Received / Agency:	**9/5/00**
Date Review Completed	**11/29/00**
Reviewer:	**Ranjit B. Mani, M.D.**

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