

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> safely and effectively. See full prescribing information for RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup>.

**RAZADYNE<sup>®</sup> ER (galantamine hydrobromide) Extended-Release Capsules, for oral use**

**RAZADYNE<sup>®</sup> (galantamine hydrobromide) Tablets, for oral use**

**RAZADYNE<sup>®</sup> (galantamine hydrobromide) Oral Solution**

Initial U.S. Approval: 2001

### INDICATIONS AND USAGE

RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> is a cholinesterase inhibitor indicated for the treatment of mild to moderate dementia of the Alzheimer's type (1)

### DOSAGE AND ADMINISTRATION

- Recommended starting dosage for RAZADYNE<sup>®</sup> ER is 8 mg/day in the morning; increase dose to an initial maintenance dose of 16 mg/day after a minimum of 4 weeks. Based upon assessment of clinical benefit and tolerability, dosage may be increased to 24 mg/day after a minimum of 4 weeks at 16 mg/day. (2.1)
- Conversion from RAZADYNE<sup>®</sup> Tablets and Oral Solution to RAZADYNE<sup>®</sup> ER should occur at the same daily dosage with the last dose of RAZADYNE<sup>®</sup> Tablets/Oral Solution taken in the evening and starting RAZADYNE<sup>®</sup> ER once daily treatment the next morning. (2.1)
- Recommended starting dosage for RAZADYNE<sup>®</sup> Tablets and Oral Solution is 4 mg twice daily; increase dose to initial maintenance dosage of 8 mg twice daily after a minimum of 4 weeks. Based upon assessment of clinical benefit and tolerability, dosage may be increased to 12 mg twice daily after a minimum of 4 weeks at 8 mg twice daily. (2.2)
- Take RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> Tablets and Oral Solution with meals. Ensure adequate fluid intake during treatment (2.2)

### DOSAGE FORMS AND STRENGTHS

- Extended-Release Capsules – 8 mg, 16 mg, 24 mg (3)
- Tablets – 4 mg, 8 mg, 12 mg (3)
- Oral Solution – 4 mg/mL (3)

### CONTRAINDICATIONS

Known hypersensitivity to galantamine hydrobromide or any excipients (4)

### WARNINGS AND PRECAUTIONS

- All patients should be considered at risk for adverse effects on cardiac conduction, including bradycardia and AV block, due to vagotonic effects on sinoatrial and atrioventricular nodes (5.2)
- Active or occult gastrointestinal bleeding: monitor, especially those with an increased risk for developing ulcers (5.3)
- Cholinomimetics may cause bladder outflow obstruction (5.4)
- Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. Patients with Alzheimer's disease should be monitored closely for seizures while taking galantamine. (5.5)
- Monitor for respiratory adverse events in patients with a history of severe asthma or obstructive pulmonary disease (5.6)

### ADVERSE REACTIONS

The most common adverse reactions (≥5%) were nausea, vomiting, diarrhea, dizziness, headache, decreased appetite, and weight decreased (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ortho-McNeil Neurologics at 1-800-526-7736 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Potential to interfere with the activity of anticholinergic medications (7.1)
- Synergistic effect expected when given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents, or cholinergic agonists (7.2)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data may cause fetal harm. (8.1)

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Revised: 06/2013

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> (galantamine hydrobromide) are indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

### **2 DOSAGE AND ADMINISTRATION**

#### **2.1 RAZADYNE<sup>®</sup> ER Extended-Release Capsules**

RAZADYNE<sup>®</sup> ER (galantamine hydrobromide) Extended-Release Capsules should be administered once daily in the morning, preferably with food.

The recommended starting dosage of RAZADYNE<sup>®</sup> ER is 8 mg/day. The dosage should be increased to the initial maintenance dose of 16 mg/day after a minimum of 4 weeks. A further increase to 24 mg/day should be attempted after a minimum of 4 weeks at 16 mg/day. Dosage increases should be based upon assessment of clinical benefit and tolerability of the previous dose.

The dosage of RAZADYNE<sup>®</sup> ER shown to be effective in a controlled clinical trial is 16-24 mg/day.

Patients currently being treated with RAZADYNE<sup>®</sup> Tablets or Oral Solution can convert to RAZADYNE<sup>®</sup> ER (extended-release capsules) by taking their last dose of RAZADYNE<sup>®</sup> Tablets or Oral Solution in the evening and starting RAZADYNE<sup>®</sup> ER once daily treatment the next morning. Converting from RAZADYNE<sup>®</sup> to RAZADYNE<sup>®</sup> ER should occur at the same total daily dosage.

#### **2.2 RAZADYNE<sup>®</sup> Immediate-Release Tablets and Oral Solution**

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

The recommended starting dosage of RAZADYNE<sup>®</sup> Tablets and Oral Solution is 4 mg twice a day (8 mg/day). The dosage should be increased to the initial maintenance dosage of 8 mg twice a day (16 mg/day) after a minimum of 4 weeks. A further increase to 12 mg twice a day (24 mg/day) should be attempted after a minimum of 4 weeks at 8 mg twice a day (16 mg/day).

Dosage increases should be based upon assessment of clinical benefit and tolerability of the previous dose.

RAZADYNE<sup>®</sup> Tablets and Oral Solution should be administered twice a day, preferably with morning and evening meals.

Patients and caregivers should be advised to ensure adequate fluid intake during treatment. If therapy has been interrupted for more than three days, the patient should be restarted at the lowest dosage and the dosage escalated to the current dose.

Caregivers should be instructed in the correct procedure for administering RAZADYNE<sup>®</sup> Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering RAZADYNE<sup>®</sup> Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

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

### **2.3 Hepatic Impairment**

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 total daily dosage should generally not exceed 16 mg/day. The use of RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> in patients with severe hepatic impairment (Child-Pugh score of 10-15) is not recommended.

### **2.4 Renal Impairment**

For patients with moderate renal impairment the dosage should generally not exceed 16 mg/day. In patients with severe renal impairment (creatinine clearance <9 mL/min), the use of RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> is not recommended.

## **3 DOSAGE FORMS AND STRENGTHS**

RAZADYNE<sup>®</sup> ER (galantamine hydrobromide) Extended-Release Capsules contain white to off-white pellets and are available in the following strengths:

8 mg white opaque, size 4 hard gelatin capsule with the inscription “GAL 8”

16 mg pink opaque, size 2 hard gelatin capsule with the inscription “GAL 16”

24 mg caramel opaque, size 1 hard gelatin capsule with the inscription “GAL 24”

RAZADYNE<sup>®</sup> Tablets are available in the following strengths:

4 mg off-white tablet imprinted with “JANSSEN” on one side and “G 4” on the other side

8 mg pink tablet imprinted with “JANSSEN” on one side and “G 8” on the other side

12 mg orange-brown tablet imprinted with “JANSSEN” on one side and “G 12” on the other side

RAZADYNE<sup>®</sup> 4 mg/mL oral solution is a clear colorless solution supplied in 100 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.5 mL, while the maximum calibrated volume is 4 mL.

#### **4 CONTRAINDICATIONS**

RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> (galantamine hydrobromide) is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulation.

#### **5 WARNINGS AND PRECAUTIONS**

##### **5.1 Anesthesia**

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

##### **5.2 Cardiovascular Conditions**

Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and AV block. 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.

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]).

##### **5.3 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 galantamine have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Galantamine, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting, diarrhea, anorexia, and weight loss. During therapy, the patient's weight should be monitored [*see Adverse Reactions (6.1)*].

## 5.4 Genitourinary Conditions

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

## 5.5 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 galantamine compared to placebo. Patients with Alzheimer's disease should be monitored closely for seizures while taking galantamine.

## 5.6 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. Respiratory function should be monitored closely for the occurrence of respiratory adverse effects.

## 5.7 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 galantamine (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 galantamine deaths appeared to result from various vascular causes (myocardial infarction, stroke, and sudden death).

Although the difference in mortality between galantamine- and placebo-treated groups in these two studies was significant, the results are highly discrepant with other studies of galantamine. 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 galantamine 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 galantamine-treated MCI subjects was also lower than that observed in galantamine-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 galantamine 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.

## 6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Anesthesia [*see Warnings and Precautions (5.1)*]
- Cardiovascular conditions [*see Warnings and Precautions (5.2)*]
- Gastrointestinal conditions [*see Warnings and Precautions (5.3)*]
- Genitourinary conditions [*see Warnings and Precautions (5.4)*]
- Neurological conditions [*see Warnings and Precautions (5.5)*]
- Pulmonary conditions [*see Warnings and Precautions (5.6)*]
- Deaths in subjects with mild cognitive impairment (MCI) [*see Warnings and Precautions (5.7)*]

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions in galantamine-treated subjects from double-blind clinical trials ( $\geq 5\%$ ) were nausea, vomiting, diarrhea, dizziness, headache, decreased appetite, and weight decreased.

The most common adverse reactions associated with discontinuation ( $\geq 1\%$ ) in galantamine-treated subjects from double-blind clinical trials were nausea (7.7%), vomiting (4.1%), decreased appetite (1.9%), and dizziness (1.6%).

The safety of the extended-release capsule and immediate-release tablet formulations of galantamine was evaluated in 2932 galantamine-treated subjects who participated in 7 placebo-controlled clinical studies and 1454 subjects in 5 open-label clinical studies with mild to moderate dementia of the Alzheimer's type. In clinical studies, the safety profile of once-daily treatment with extended-release galantamine was similar in frequency and nature to that seen with tablets. The information presented in this section was derived from pooled double-blind studies and from pooled open-label data.

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of galantamine based on the comprehensive assessment of the available adverse event information. A causal relationship with galantamine cannot be reliably established in individual cases.

### Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials

Table 1 lists the adverse drug reactions reported in  $\geq 1\%$  of galantamine-treated subjects in 7 placebo-controlled, double-blind clinical trials.

**Table 1. Adverse Drug Reactions Reported by  $\geq 1\%$  of Galantamine-Treated Subjects in 7 Placebo-Controlled, Double-Blind Clinical Trials**

<b>System/Organ Class</b>	<b>Galantamine (n=2932)</b>	<b>Placebo (n=1525)</b>
Adverse Reaction	%	%
<b>Metabolism and Nutrition Disorders</b>		
Decreased appetite	5.2	1.4
Anorexia	3.8	1.0
<b>Psychiatric Disorders</b>		
Depression	4.2	2.9
<b>Nervous System Disorders</b>		
Dizziness	8.9	4.6
Headache	7.6	5.4
Tremor	2.0	0.8
Syncope	1.8	0.7
Lethargy	1.7	0.7
Somnolence	1.7	0.8
<b>Cardiac Disorders</b>		
Bradycardia	1.2	0.3
<b>Gastrointestinal Disorders</b>		
Nausea	25.0	7.6
Vomiting	12.8	3.1
Diarrhea	9.0	6.3
Abdominal pain	2.4	0.9
Abdominal pain upper	2.0	1.4
Dyspepsia	1.8	1.3
Stomach discomfort	1.6	0.6
Abdominal discomfort	1.0	0.4
<b>Skin and Subcutaneous Tissue Disorders</b>		
Hyperhidrosis	1.2	0.7
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Muscle spasms	1.5	0.8
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	4.0	2.2
Asthenia	2.3	1.7
Malaise	1.4	0.7
<b>Investigations</b>		
Weight decreased	5.1	1.4

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 RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> with food, the use of anti-emetic medication, and ensuring adequate fluid intake may reduce the impact of these events [*see Dosage and Administration (2) and Patient Counseling Information (17)*].

#### Other Adverse Reactions Observed in Clinical Trials of Galantamine

The following adverse reactions occurred in <1% of all galantamine-treated subjects (N=2932) in the above double-blind, placebo-controlled clinical trial data sets. In addition, the following also includes all adverse reactions reported at any frequency rate in subjects (N=1454) who

participated in open-label studies. Adverse reactions listed in Table 1 above were not included below:

*Metabolism and Nutrition Disorders:* Dehydration

*Nervous System Disorders:* Dysgeusia, Hypersomnia, Paresthesia

*Eye Disorders:* Vision blurred

*Cardiac Disorders:* Atrioventricular block first degree, Palpitations, Sinus bradycardia, Supraventricular extrasystoles

*Vascular Disorders:* Flushing, Hypotension

*Gastrointestinal Disorders:* Retching

*Musculoskeletal and Connective Tissue Disorders:* Muscular weakness

*Injury, Poisoning and Procedural Complications:* Fall

#### Discontinuations Due to Adverse Reactions

In the 7 placebo-controlled studies of adults, 379 (12.9%) galantamine-treated patients (N=2932) and 42 (2.8%) placebo patients (N=1525) discontinued due to an adverse reaction. Those events with an incidence of  $\geq 0.5\%$  in the galantamine-treated patients included nausea (225, 7.7%), vomiting (119, 4.1%), decreased appetite (56, 1.9%), dizziness (48, 1.6%), diarrhea (27, 0.9%), headache (26, 0.9%) weight decreased (24, 0.8%), and abdominal pain (15, 0.5%). Those events with an incidence of  $\geq 0.5\%$  in placebo patients included nausea (14, 0.9%) and dizziness (8, 0.5%).

In the 5 open-label studies, 103 (7.1%) patients (N=1454) discontinued due to an adverse reaction. Those events with an incidence of  $\geq 0.5\%$  included nausea (43, 3.0%), vomiting (23, 1.6%), decreased appetite (13, 0.9%), headache (12, 0.8%), weight decreased (9, 0.6%), dizziness (8, 0.6%), and diarrhea (7, 0.5%).

## 6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup>. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency:

*Immune System Disorders:* Hypersensitivity

*Psychiatric Disorders:* Hallucination, Hallucination visual, Hallucination auditory

*Ear and Labyrinth Disorders:* Tinnitus

*Vascular Disorders:* Hypertension

*Hepatobiliary Disorders:* Hepatitis, Hepatic enzyme increased

## **7 DRUG INTERACTIONS**

### **7.1 Use with Anticholinergics**

Galantamine has the potential to interfere with the activity of anticholinergic medications [*see Clinical Pharmacology (12.3)*].

### **7.2 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 [*see Clinical Pharmacology (12.3)*].

### **7.3 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 [*see Clinical Pharmacology (12.3)*].

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 pharmacokinetics 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 500 mg QID for 4 days, affected the AUC of galantamine minimally (10% increase).

#### *Paroxetine*

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

#### *Memantine*

Memantine, an N-methyl-D-aspartate receptor antagonist, at a dose of 10 mg BID, had no effect on the pharmacokinetics of galantamine (16 mg/day) at steady state.

## 7.4 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 [see *Clinical Pharmacology (12.3)*].

### 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 mg once daily) when they were coadministered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. In studies conducted in animals, administration of galantamine during pregnancy resulted in developmental toxicity (increased incidence of morphological abnormalities and decreased growth in offspring) at doses similar to or greater than those used clinically. RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In rats, administration of galantamine (oral doses of 2, 8, or 16 mg/kg/day), from day 14 (females) or day 60 (males) prior to mating and continuing in females through the period of organogenesis, resulted in an increased incidence of fetal skeletal variations at the two highest doses. The no-effect dose for embryo-fetal developmental toxicity in rats (2 mg/kg/day) is approximately equal to the maximum recommended human dose (MRHD of 24 mg/day) on a body surface area (mg/m<sup>2</sup>) basis. When galantamine (oral doses of 4, 12, 28, or 48 mg/kg/day) was administered to pregnant rabbits throughout the period of organogenesis, small increases in fetal visceral malformations and skeletal variations were observed at the highest dose. The no-effect dose for embryo-fetal developmental toxicity in rabbits (28 mg/kg/day) is approximately 20 times the MRHD on a mg/m<sup>2</sup> basis. In a study in which pregnant rats were orally dosed with galantamine (2, 8, or 16 mg/kg/day) from the beginning of organogenesis through day 21 post-partum, pup weights were decreased at birth and during the lactation period at the two highest doses. The no-effect dose for pre- and postnatal developmental toxicity in rats (2 mg/kg/day) is approximately equal to the MRHD on a mg/m<sup>2</sup> basis.

### 8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> is administered to a nursing woman.

### 8.4 Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

### 8.5 Geriatric Use

Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age. Seven double-blind, placebo-controlled clinical trials and 5 open-label trials in a total of 4474 patients have investigated RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> in the treatment of mild to moderate dementia of the Alzheimer's type [*see Adverse Reactions (6.1) and Clinical Studies (14)*]. The mean age of patients enrolled in these clinical studies was 75 years; 78% of these patients were between 65 and 84 years of age, and 11% of patients were 85 years of age or older.

### 8.6 Hepatic Impairment

In patients with moderately impaired hepatic function, dose titration should proceed cautiously [*see Clinical Pharmacology (12.3) and Dosage and Administration (2.3)*]. The use of RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> in patients with severe hepatic impairment is not recommended.

### 8.7 Renal Impairment

In patients with moderately impaired renal function, dose titration should proceed cautiously [*see Clinical Pharmacology (12.3) and Dosage and Administration (2.4)*]. In patients with severely impaired renal function ( $CL_{cr} < 9$  mL/min) the use of RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> is not recommended.

## 10 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.

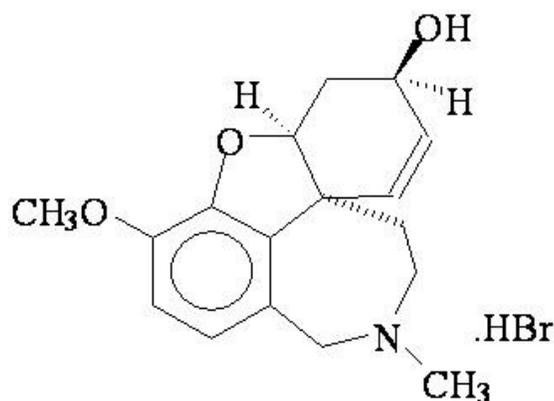
As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous 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 RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> (galantamine hydrobromide) overdose. Intravenous atropine sulfate 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 coadministered with quaternary anticholinergics. It is not known whether galantamine 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.

In one postmarketing report, one patient who had been taking 4 mg of galantamine daily for a week inadvertently ingested eight 4 mg tablets (32 mg total) on a single day. Subsequently, she developed bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness for which she required hospital treatment. Two additional cases of accidental ingestion of 32 mg (nausea, vomiting, and dry mouth; nausea, vomiting, and substernal chest pain) and one of 40 mg (vomiting), resulted in brief hospitalizations for observation with full recovery. One patient, who was prescribed 24 mg/day and had a history of hallucinations over the previous two years, mistakenly received 24 mg twice daily for 34 days and developed hallucinations requiring hospitalization. Another patient, who was prescribed 16 mg/day of oral solution, inadvertently ingested 160 mg (40 mL) and experienced sweating, vomiting, bradycardia, and near-syncope one hour later, which necessitated hospital treatment. His symptoms resolved within 24 hours.

## 11 DESCRIPTION

RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> (galantamine hydrobromide) is galantamine hydrobromide, a reversible, competitive acetylcholinesterase inhibitor. Galantamine hydrobromide 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<sub>17</sub>H<sub>21</sub>NO<sub>3</sub> •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:



RAZADYNE<sup>®</sup> ER is available in opaque hard gelatin extended-release capsules of 8 mg (white), 16 mg (pink), and 24 mg (caramel) containing galantamine hydrobromide, equivalent to respectively 8, 16 and 24 mg galantamine base. Inactive ingredients include gelatin, diethyl phthalate, ethylcellulose, hypromellose, polyethylene glycol, titanium dioxide and sugar spheres (sucrose and starch). The 16 mg capsule also contains red ferric oxide. The 24 mg capsule also contains red ferric oxide and yellow ferric oxide.

RAZADYNE<sup>®</sup> for oral use is available in circular biconvex film-coated immediate release tablets of 4 mg (off-white), 8 mg (pink), 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, hypromellose, 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.

RAZADYNE<sup>®</sup> is also available as a 4 mg/mL oral solution. The inactive ingredients for this solution are methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium saccharin, sodium hydroxide and purified water.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 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.

### **12.3 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 acetylcholinesterase 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 bioavailability 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 *Drug Interactions (7.3)*]. 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  $^3\text{H}$ -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.

RAZADYNE<sup>®</sup> ER 24 mg Extended-Release Capsules administered once daily under fasting conditions are bioequivalent to RAZADYNE<sup>®</sup> Tablets 12mg twice daily with respect to  $\text{AUC}_{24\text{h}}$  and  $C_{\min}$ . The  $C_{\max}$  and  $T_{\max}$  of the extended-release capsules were lower and occurred later, respectively, compared with the immediate-release tablets, with  $C_{\max}$  about 25% lower and median  $T_{\max}$  occurring about 4.5 – 5.0 hours after dosing. Dose-proportionality is observed for RAZADYNE<sup>®</sup> ER Extended-Release Capsules over the dose range of 8 to 24 mg daily and steady state is achieved within a week. There was no effect of age on the pharmacokinetics of RAZADYNE<sup>®</sup> ER Extended-Release Capsules. CYP2D6 poor metabolizers had drug exposures that were approximately 50% higher than for extensive metabolizers.

There are no appreciable differences in pharmacokinetic parameters when RAZADYNE<sup>®</sup> ER Extended-Release Capsules are given with food compared to when they are given in the fasted state.

## Specific 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%  $AUC_{\infty}$  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 tablets, 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 *Use in Specific Populations (8.6) and Dosage and Administration (2.3)*].

### *Renal Impairment*

Following a single 8 mg dose of galantamine tablets, AUC increased by 37% and 67% in moderate and severely renal-impaired patients compared to normal volunteers [see *Use in Specific Populations (8.7) and Dosage and Administration (2.4)*].

### *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 galantamine, 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 galantamine.

## 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.

### *Effect of Other Drugs on the Metabolism of Galantamine*

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 coadministration of ketoconazole and paroxetine. As co-administered with erythromycin, another CYP3A4 inhibitor, the galantamine AUC increased only 10%. Population pharmacokinetics 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<sub>2</sub>-antagonists demonstrated that ranitidine did not affect the pharmacokinetics of galantamine, and cimetidine increased the galantamine AUC by approximately 16%.

A multiple dose pharmacokinetic study with concurrent administration of memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, demonstrated that co-administration of memantine in a dose of 10 mg BID did not affect the pharmacokinetic profile of galantamine (16 mg daily) at steady state.

### *Effect of Galantamine 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 or CYP2E1. This indicates 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.

## **13 NON-CLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### **Carcinogenesis**

In a 24-month oral carcinogenicity study in rats, an increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the MRHD of 24 mg/day on a mg/m<sup>2</sup> basis or 6 times on a plasma exposure [AUC] basis) and 30 mg/kg/day (12 times MRHD on a mg/m<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> and AUC basis).

Galantamine was not carcinogenic in a 6-month carcinogenicity study in transgenic (P 53-deficient) mice at oral doses up to 20 mg/kg/day, or in a 24-month carcinogenicity study in mice at oral doses up to 10 mg/kg/day (equivalent to the MRHD on a plasma AUC basis).

### Mutagenesis

Galantamine was negative in a battery of *in vitro* (bacterial reverse mutation, mouse lymphoma *tk*, and chromosomal aberration in mammalian cells) and *in vivo* (mouse micronucleus) genotoxicity assays.

### Impairment of Fertility

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

## 14 CLINICAL STUDIES

The effectiveness of galantamine as a treatment for Alzheimer's disease is demonstrated by the results of 5 randomized, double-blind, placebo-controlled clinical investigations in patients with probable Alzheimer's disease, 4 with the immediate-release tablet and 1 with the extended-release capsule [diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination scores that were  $\geq 10$  and  $\leq 24$ ]. Doses studied with the tablet formulation were 8-32 mg/day given as twice daily doses. In 3 of the 4 studies with the tablet, 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 these 4 galantamine 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.

### 14.1 Study Outcome Measures

In each study, the primary effectiveness of galantamine 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 that required the use of caregiver information (CIBIC-plus).

The ability of galantamine 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 using the tablet formulation 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 galantamine trials was approximately 4.5 units per year.

The ability of galantamine 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 cannot 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.

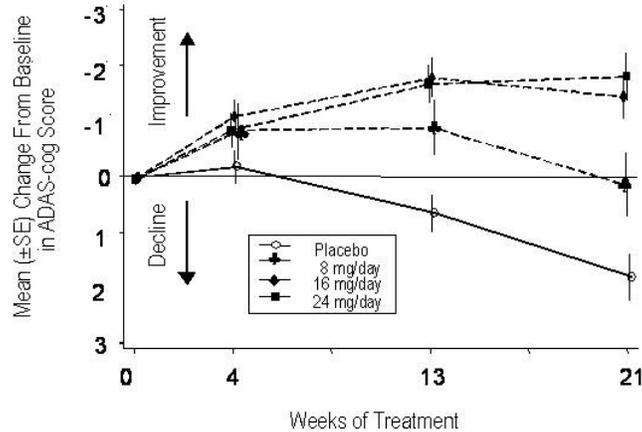
## **14.2 Immediate-Release Tablets**

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

In a study of 21 weeks duration, 978 patients were randomized to doses of 8, 16, or 24 mg of galantamine per day, or to placebo, each given in 2 divided doses. Treatment was initiated at 8 mg/day for all patients randomized to galantamine, 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 galantamine).

#### *Effects on the ADAS-cog*

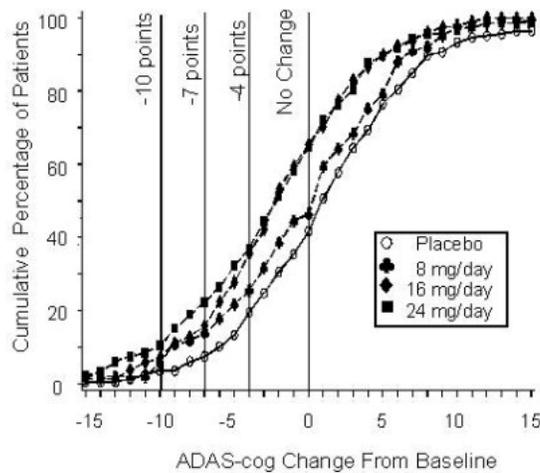
Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all four dose groups over the 21 weeks of the study. At 21 weeks of treatment, the mean differences in the ADAS-cog change scores for the galantamine-treated patients compared to the patients on placebo were 1.7, 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**

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 galantamine groups are more likely to show the greater improvements.

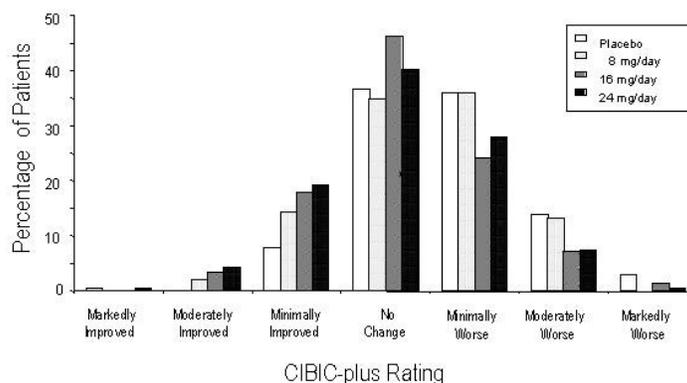


**Figure 2: Cumulative Percentage of Patients Completing 21 Weeks of Double-Blind Treatment With Specified Changes From Baseline in ADAS-cog Scores. The Percentages of Randomized Patients Who Completed the Study Were: Placebo 84%, 8 mg/day 77%, 16 mg/day 78% and 24 mg/day 78%.**

Treatment	Change in ADAS-cog			
	-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 galantamine-placebo differences for these groups of patients in mean rating were 0.15, 0.41 and 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.



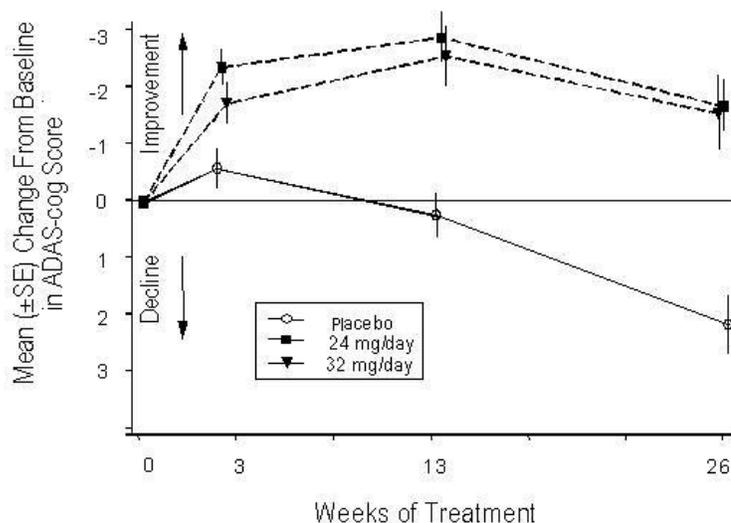
**Figure 3: Distribution of CIBIC-plus Ratings at Week 21**

### 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 galantamine 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 galantamine-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.

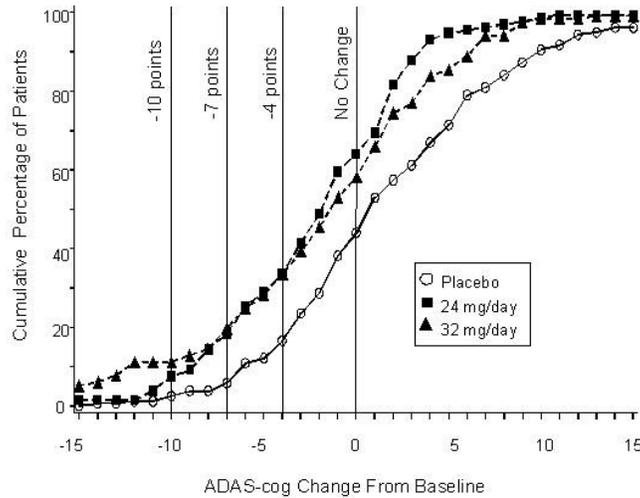


**Figure 4: Time-Course of the Change From Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment**

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 galantamine and placebo have a wide range of responses, but that the galantamine 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.

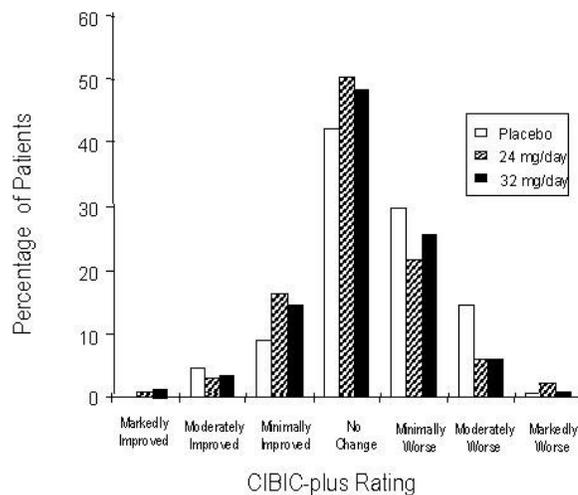
Treatment	Change in ADAS-cog			
	-10	-7	-4	-0
Placebo	2.1%	5.7%	16.6 %	43.9%
24 mg/day	7.6%	18.3%	33.6%	64.1%
32 mg/day	11.1%	19.7%	33.3%	58.1%



**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%.

### 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 galantamine-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 galantamine, 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 at Week 26

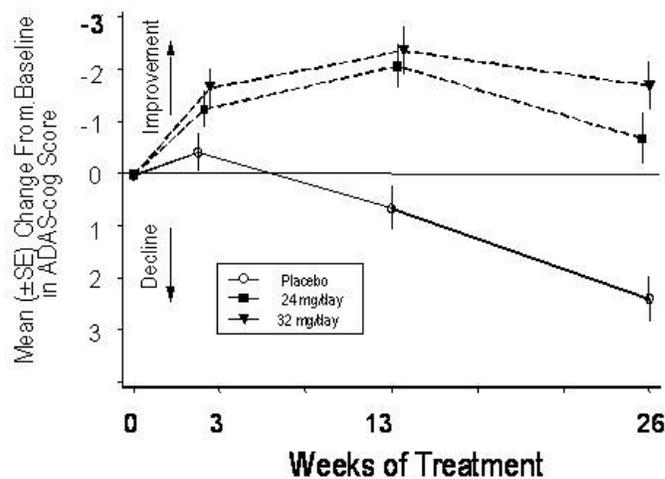
### International Twenty-Six Week Fixed-Dose Study

In a study of 26 weeks duration identical in design to the USA 26-Week Fixed-Dose Study, 653 patients were randomized to either a dose of 24 mg or 32 mg of galantamine 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

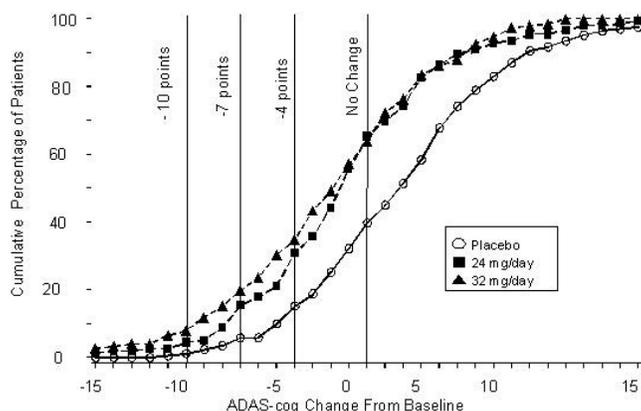
Figure 7 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the galantamine-treated patients compared to the patients on placebo were 3.1 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 galantamine and placebo have a wide range of responses, but that the galantamine groups are more likely to show the greater improvements.

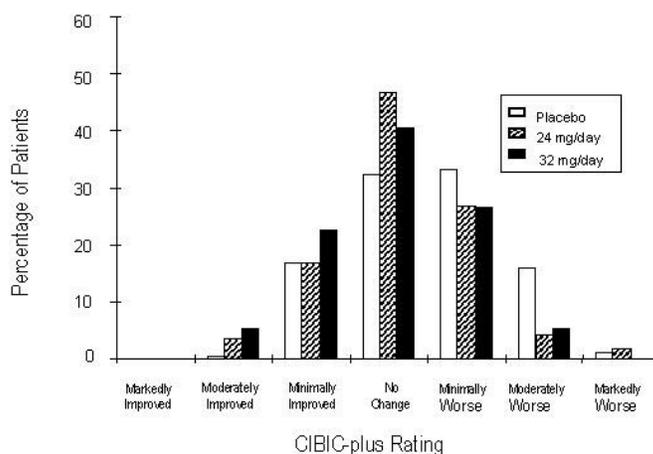


**Figure 8:** Cumulative Percentage of Patients Completing 26 Weeks of Double-Blind Treatment With Specified Changes From Baseline in ADAS-cog Scores. The Percentages of Randomized Patients Who Completed the Study Were: Placebo 87%, 24 mg/day 80%, and 32 mg/day 75%.

Treatment	Change in ADAS-cog			
	-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 galantamine-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 galantamine respectively. The mean ratings for the galantamine groups were statistically significantly superior to placebo, but were not significantly different from each other.



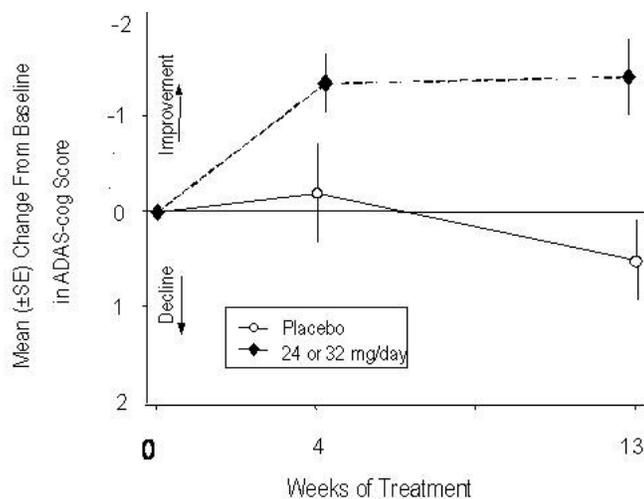
**Figure 9:** Distribution of CIBIC-plus Rating at Week 26

### 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 galantamine 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

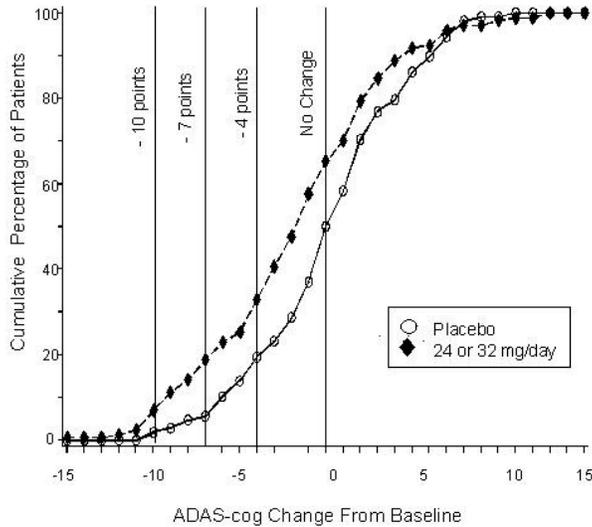
Figure 10 illustrates the time course for the change from baseline in ADAS-cog scores for both dose groups over the 13 weeks of the study. At 13 weeks of treatment, the mean difference in the ADAS-cog change scores for the treated patients compared to the patients on placebo was 1.9. Galantamine at a 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 galantamine and placebo have a wide range of responses, but that the galantamine group is more likely to show the greater improvement.

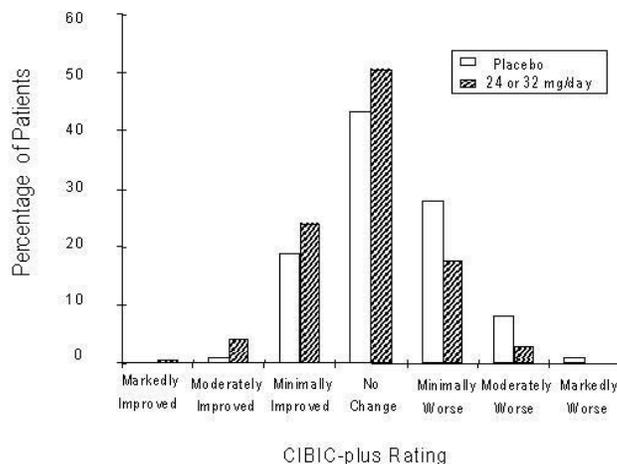


**Figure 11: Cumulative Percentage of Patients Completing 13 Weeks of Double-Blind Treatment With Specified Changes from Baseline in ADAS-cog Scores. The Percentages of Randomized Patients Who Completed the Study Were: Placebo 90%, 24-32 mg/day 67%.**

Treatment	Change in ADAS-cog			
	-10	-7	-4	-0
Placebo	1.9%	5.6%	19.4 %	50.0%
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 13 weeks of treatment. The mean galantamine-placebo differences for the group of patients in the mean rating of change from baseline were 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 13**

## Age, Gender and Race

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

### 14.3 Extended-Release Capsules

The efficacy of galantamine extended-release capsules was studied in a randomized, double-blind, placebo-controlled trial which was 6 months in duration, and had an initial 4-week dose-escalation phase. In this trial, patients were assigned to one of 3 treatment groups: Galantamine extended-release capsules in a flexible dose of 16 to 24 mg once daily; galantamine tablets in a flexible dose of 8 to 12 mg twice daily; and placebo. The primary efficacy measures in this study were the ADAS-cog and CIBIC-plus. On the protocol-specified primary efficacy analysis at Month 6, a statistically significant improvement favoring galantamine extended-release capsules over placebo was seen for the ADAS-cog, but not for the CIBIC-plus. Galantamine extended-release capsules showed a statistically significant improvement when compared with placebo on the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale, a measure of function, and a secondary efficacy measure in this study. The effects of both galantamine extended-release capsules and galantamine tablets on the ADAS-cog, CIBIC-plus, and ADCS-ADL were similar in this study.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

RAZADYNE<sup>®</sup> ER (galantamine hydrobromide) Extended-Release Capsules are supplied as follows:

8 mg capsules – bottles of 30 NDC 50458-387-30

16 mg capsules – bottles of 30 NDC 50458-388-30

24 mg capsules – bottles of 30 NDC 50458-389-30

RAZADYNE<sup>®</sup> (galantamine hydrobromide) Tablets are supplied as follows:

4 mg tablets – bottles of 60 NDC 50458-396-60

8 mg tablets – bottles of 60 NDC 50458-397-60

12 mg tablets – bottles of 60 NDC 50458-398-60

RAZADYNE<sup>®</sup> (galantamine hydrobromide) Oral Solution is supplied as follows:

4 mg/mL oral solution – 100 mL bottle NDC 50458-490-10

### Storage and Handling

RAZADYNE<sup>®</sup> ER Extended-Release Capsules should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

RAZADYNE<sup>®</sup> Tablets should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

RAZADYNE<sup>®</sup> Oral Solution should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. DO NOT FREEZE.

Keep out of reach of children.

## **17 PATIENT COUNSELING INFORMATION**

### **General Dosing Guidance**

Caregivers should be instructed about the recommended dosage and administration of RAZADYNE<sup>®</sup> ER and RAZADYNE<sup>®</sup> (galantamine hydrobromide). RAZADYNE<sup>®</sup> ER Extended-Release Capsules should be administered once daily in the morning, preferably with food. RAZADYNE<sup>®</sup> Tablets and Oral Solution should be administered twice per day, preferably with the morning and evening meals. Dose escalation (dose increases) should follow a minimum of four weeks at prior dose. If therapy has been interrupted for more than three days, the patient should be restarted with the lowest dose and then re-titrated to an appropriate dosage [*see Dosage and Administration (2)*].

Patients and caregivers should be advised to ensure adequate fluid intake during treatment [*see Dosage and Administration (2)*].

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.

### **Oral Solution Instruction Sheet**

Caregivers should be instructed in the correct procedure for administering RAZADYNE<sup>®</sup> Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering RAZADYNE<sup>®</sup> Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

Product of Belgium.

RAZADYNE<sup>®</sup> ER Extended-Release Capsules contents are manufactured by:

Janssen Pharmaceutica N.V.

Olen, Belgium.

RAZADYNE<sup>®</sup> ER Extended-Release Capsules and RAZADYNE<sup>®</sup> Tablets are manufactured by:

Janssen Ortho LLC

Gurabo, Puerto Rico 00778

RAZADYNE<sup>®</sup> Oral Solution is manufactured by:

Janssen Pharmaceutica N.V.

Beerse, Belgium

RAZADYNE<sup>®</sup> ER Extended-Release Capsules, RAZADYNE<sup>®</sup> Tablets, and RAZADYNE<sup>®</sup> Oral Solution are manufactured for:

Janssen Pharmaceuticals, Inc.

Titusville, NJ 08560

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