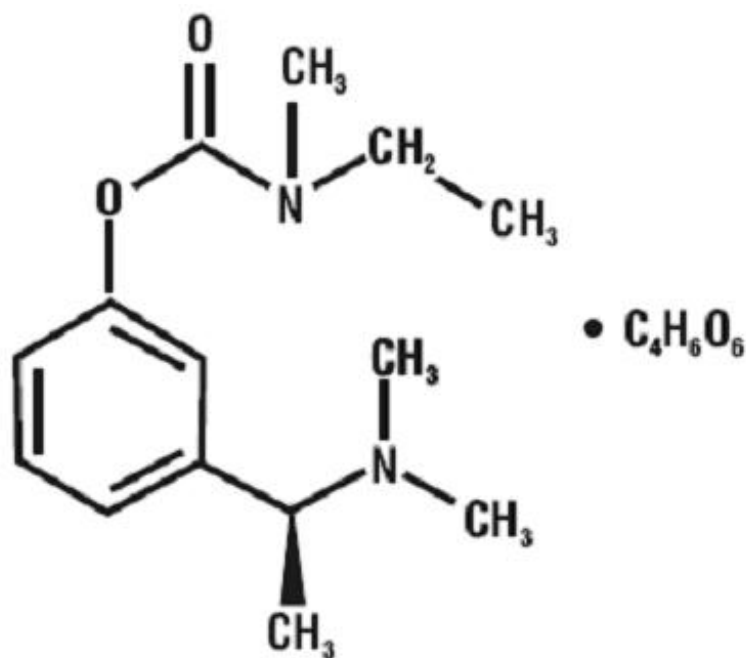


RIVASTIGMINE TARTRATE - rivastigmine tartrate capsule
Physicians Total Care, Inc.

Rivastigmine Tartrate Capsules

DESCRIPTION

Rivastigmine tartrate is a reversible cholinesterase inhibitor and is known chemically as (S)-N-Ethyl-N-methyl-3-[1-(dimethylamino) ethyl]-phenyl carbamate hydrogen-(2R,3R)-tartrate. Rivastigmine tartrate is commonly referred to in the pharmacological literature as SDZ ENA 713 or ENA 713. It has a molecular formula of $C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$ (hydrogen tartrate salt-hta salt) and a molecular weight of 400.43 (hta salt). Rivastigmine tartrate is a white to off-white, fine crystalline powder that is very soluble in water, soluble in ethanol and acetonitrile, slightly soluble in n-octanol and very slightly soluble in ethyl acetate. The distribution coefficient at 37°C in n-octanol/phosphate buffer solution pH 7 is 3.



Rivastigmine Tartrate Capsules contain rivastigmine tartrate, equivalent to 1.5 mg, 3 mg, 4.5 mg and 6 mg of rivastigmine base for oral administration. Inactive ingredients are magnesium stearate, microcrystalline cellulose, and colloidal silicon dioxide. Each hard-gelatin capsule contains gelatin, titanium dioxide, D & C Red # 28 (1.5 mg), D & C Yellow # 10 (1.5 mg), FD & C Yellow # 6 (1.5 mg, 3 mg, 6 mg), FD & C Red # 40 (6 mg), red iron oxide (4.5 mg, 6 mg) and yellow iron oxide (4.5 mg, 6 mg).

The imprinting ink contains shellac, dehydrated alcohol, butyl alcohol, propylene glycol, strong ammonia solution, potassium hydroxide and black iron oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Pathological changes in Dementia of the Alzheimer's type and Dementia associated with Parkinson's disease involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are thought to be intricately involved in memory, attention, learning, and other cognitive processes. While the precise mechanism of rivastigmine'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 proposed mechanism is correct, Rivastigmine Tartrate Capsules' effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process. After a 6 mg dose of rivastigmine, anticholinesterase activity is present in CSF for about 10 hours, with a maximum inhibition of about 60% 5 hours after dosing.

In vitro and *in vivo* studies demonstrate that the inhibition of cholinesterase by rivastigmine is not affected by the concomitant administration of memantine, an N-methyl-D-aspartate receptor antagonist.

Clinical Trial Data

Dementia of the Alzheimer's type

The effectiveness of Rivastigmine Tartrate Capsules as a treatment for Alzheimer's Disease is demonstrated by the results of 2 randomized, double-blind, placebo-controlled clinical investigations in patients with Alzheimer's Disease [diagnosed by NINCDS-ADRDA and DSM-IV criteria, Mini-Mental State Examination (MMSE) ≥ 10 and ≤ 26 , and the Global Deterioration Scale (GDS)]. The mean age of patients participating in Rivastigmine Tartrate Capsules trials was 73 years with a range of 41 to 95. Approximately 59% of patients were women and 41% were men. The racial distribution was Caucasian 87%, Black 4% and Other races 9%.

Study Outcome Measures: In each study, the effectiveness of Rivastigmine Tartrate Capsules was evaluated using a dual outcome assessment strategy.

The ability of Rivastigmine Tartrate Capsules to improve cognitive performance was assessed with the cognitive subscale 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 23 units, with a range from 1 to 61. 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 Rivastigmine Tartrate Capsule trials was approximately 3 to 8 units per year.

The ability of Rivastigmine Tartrate Capsules to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change (CIBIC) 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

Rivastigmine Tartrate Capsules trials was a structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of three domains: patient cognition, behavior and functioning, including assessment of activities of daily living. It represents the assessment of a skilled clinician using validated scales based on his/her observation at interviews conducted separately with the patient and the caregiver familiar with the behavior of the patient over the interval rated. The CIBIC-Plus is scored as a 7 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 or other global methods.

U.S. 26-Week Study

In a study of 26 weeks duration, 699 patients were randomized to either a dose range of 1 to 4 mg or 6 to 12 mg of Rivastigmine Tartrate Capsules per day or to placebo, each given in divided doses. The 26-week study was divided into a 12-week forced dose titration phase and a 14-week maintenance phase. The patients in the active treatment arms of the study were maintained at their highest tolerated dose within the respective range.

Effects on the ADAS-cog: Figure 1 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 Rivastigmine Tartrate Capsules -treated patients compared to the patients on placebo were 1.9 and 4.9 units for the 1 to 4 mg and 6 to 12 mg treatments, respectively. Both treatments were statistically significantly superior to placebo and the 6 to 12 mg/day range was significantly superior to the 1 to 4 mg/day range.

Figure 1: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

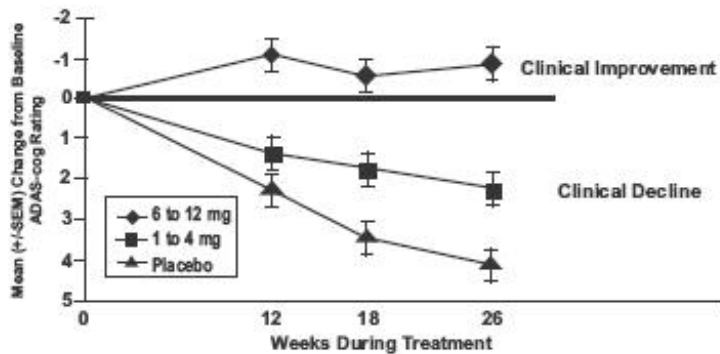
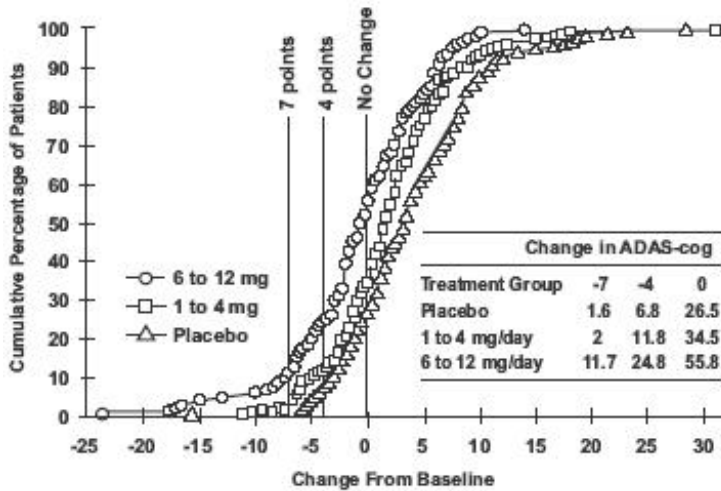


Figure 2 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified 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 Rivastigmine Tartrate Capsules and placebo have a wide range of responses, but that the Rivastigmine Tartrate Capsules 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.

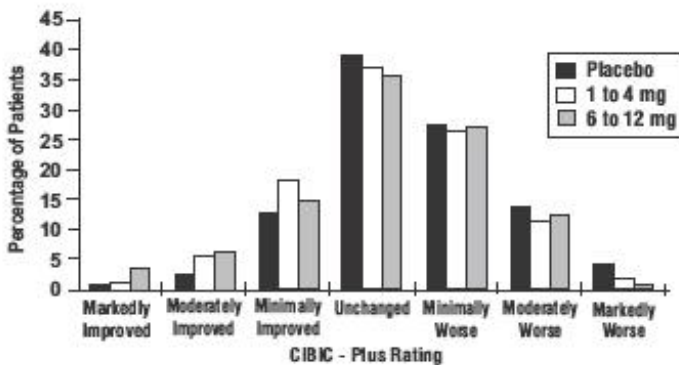
Figure 2: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 84%, 1 to 4 mg 85%, and 6 to 12 mg 65%.



Effects on the CIBIC-Plus:

Figure 3 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean Rivastigmine Tartrate Capsules -placebo differences for these groups of patients in the mean rating of change from baseline were 0.32 units and 0.35 units for 1 to 4 mg and 6 to 12 mg of Rivastigmine Tartrate Capsules, respectively. The mean ratings for the 6 to 12 mg/day and 1 to 4 mg/day groups were statistically significantly superior to placebo. The differences between the 6 to 12 mg/day and the 1 to 4 mg/day groups were statistically significant.

Figure 3: Frequency Distribution of CIBIC-Plus Scores at Week 26



Global 26-Week Study

In a second study of 26 weeks duration, 725 patients were randomized to either a dose range of 1 to 4 mg or 6 to 12 mg of Rivastigmine Tartrate Capsules per day or to placebo, each given in divided doses. The 26-week study was divided into a 12-week forced dose titration phase and a 14-week maintenance phase. The patients in the active treatment arms of the study were maintained at their highest tolerated dose within the respective range.

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 Rivastigmine Tartrate Capsules -treated patients compared to the patients on placebo were 0.2 and 2.6 units for the 1 to 4 mg and 6 to 12 mg treatments, respectively. The 6 to 12 mg/day group was statistically significantly superior to placebo, as well as to the 1 to 4 mg/day group. The difference between the 1 to 4 mg/day group and placebo was not statistically significant.

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

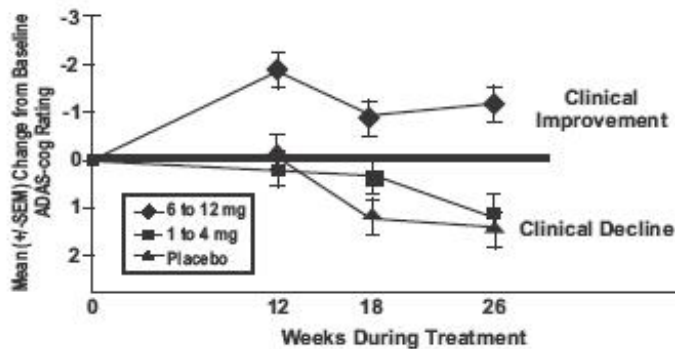
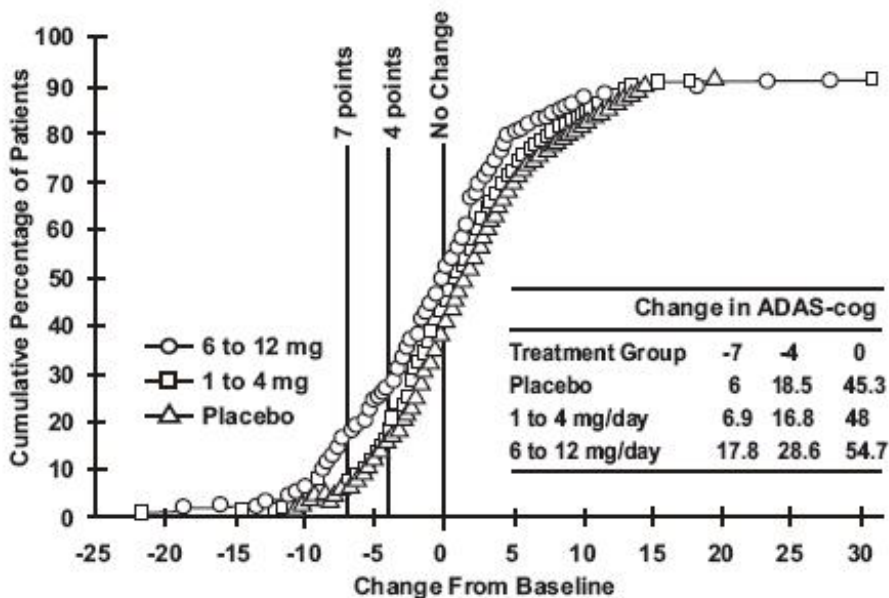


Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Similar to the U.S. 26-week study, the curves demonstrate that both patients assigned to Rivastigmine Tartrate Capsules and placebo have a wide range of responses, but that the 6 to 12 mg/day Rivastigmine Tartrate Capsules group is more likely to show the greater improvements.

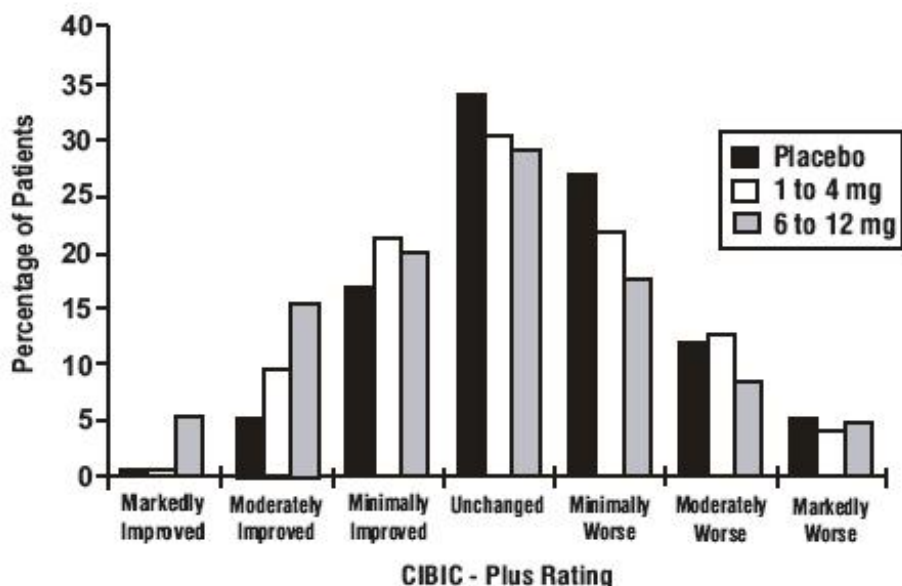
Figure 5: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 87%, 1 to 4 mg 86%, and 6 to 12 mg 67%.



Effects on the CIBIC-Plus:

Figure 6 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean Rivastigmine Tartrate Capsules -placebo differences for these groups of patients for the mean rating of change from baseline were 0.14 units and 0.41 units for 1 to 4 mg and 6 to 12 mg of Rivastigmine Tartrate Capsules, respectively. The mean ratings for the 6 to 12 mg/day group was statistically significantly superior to placebo. The comparison of the mean ratings for the 1 to 4 mg/day group and placebo group was not statistically significant.

Figure 6: Frequency Distribution of CIBIC-Plus Scores at Week 26



U.S. Fixed Dose Study

In a study of 26 weeks duration, 702 patients were randomized to doses of 3, 6, or 9 mg/day of Rivastigmine Tartrate Capsules or to placebo, each given in divided doses. The fixed-dose study design, which included a 12-week forced titration phase and a 14-week maintenance phase, led to a high dropout rate in the 9 mg/day group because of poor tolerability. At 26 weeks of treatment, significant differences were observed for the ADAS-cog mean change from baseline for the 9 mg/day and 6 mg/day groups, compared to placebo. No significant differences were observed between any of the Rivastigmine Tartrate Capsules dose groups and placebo for the analysis of the CIBIC-Plus mean rating of change. Although no significant differences were observed between Rivastigmine Tartrate Capsules treatment groups, there was a trend toward numerical superiority with higher doses.

Dementia Associated with Parkinson's disease (PDD)

International Twenty-Four-Week Study

The effectiveness of Rivastigmine Tartrate Capsules as a treatment for dementia associated with Parkinson's disease is demonstrated by the results of one randomized, double-blind, placebo-controlled clinical investigation in patients with mild to moderate dementia, with onset at least 2 years after the initial diagnosis of idiopathic Parkinson's disease. The diagnosis of idiopathic Parkinson's Disease was based on the United Kingdom Parkinson's Disease Society Brain Bank clinical criteria. The diagnosis of dementia was based on the criteria stipulated under the DSM-IV category "Dementia Due To Other General Medical Condition" (code 294.1x), but patients were not required to have a distinctive pattern of cognitive deficits as part of the dementia. Alternate causes of dementia were excluded by clinical history, physical and neurological examination, brain imaging, and relevant blood

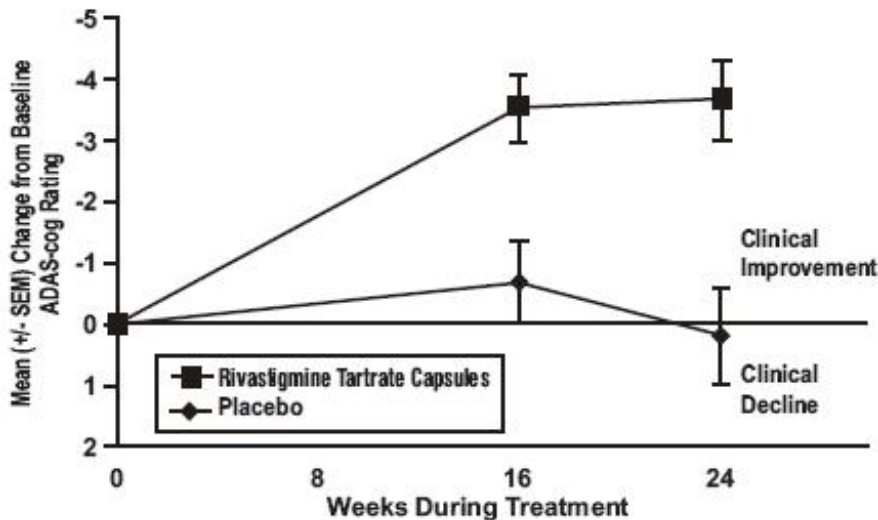
tests. Patients enrolled in the study had a MMSE score ≥ 10 and ≤ 24 at entry. The mean age of patients participating in this trial was 72.7 years with a range of 50 – 91. Approximately, 35.1% of patients were women and 64.9% of patients were men. The racial distribution was 99.6% Caucasian and Other races 0.4%.

Study Outcome Measures: This study used a dual outcome assessment strategy to evaluate the effectiveness of Rivastigmine Tartrate Capsules. The ability of Rivastigmine Tartrate Capsules to improve cognitive performance was assessed with the ADAS-cog. The ability of Rivastigmine Tartrate Capsules to produce an overall clinical effect was assessed using the Alzheimer’s Disease Cooperative Study – Clinician’s Global Impression of Change (ADCS-CGIC). The ADCS-CGIC is a more standardized form of CIBIC-Plus and is also 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."

Study Results: In this study, 541 patients were randomized to a dose range of 3 – 12 mg of Rivastigmine Tartrate Capsules per day or to placebo in a ratio of 2:1, given in divided doses. The 24-week study was divided into a 16-week titration phase and an 8-week maintenance phase. The patients in the active treatment arm of the study were maintained at their highest tolerated dose within the specified dose range.

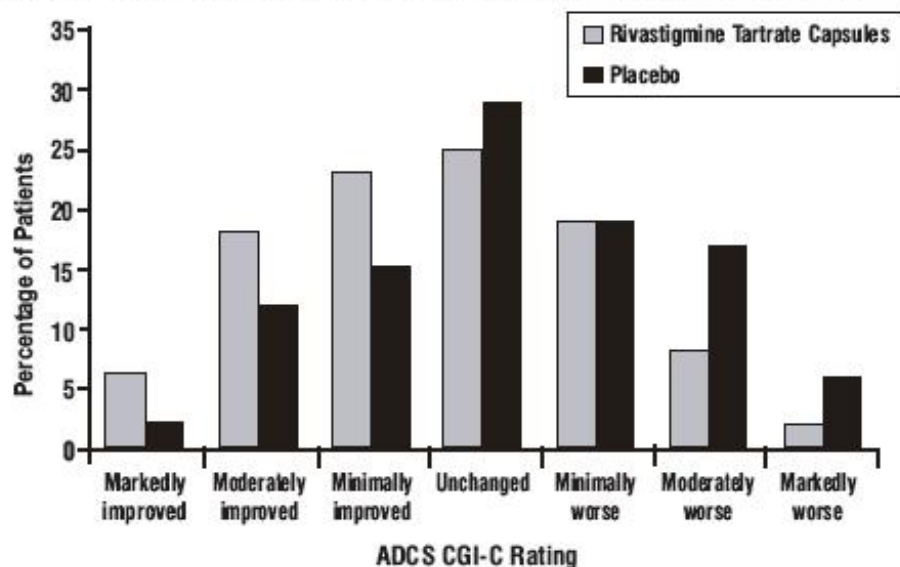
Effects on the ADAS-cog: Figure 7 illustrates the time course for the change from baseline in ADAS-cog scores for both treatment groups over the 24 week study. At 24 weeks of treatment, the mean difference in the ADAS-cog change scores for the Rivastigmine Tartrate Capsules-treated patients compared to the patients on placebo was 3.8 points. This treatment difference was statistically significant in favor of Rivastigmine Tartrate Capsules when compared to placebo.

Figure 7: Time course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks Of Treatment



Effects on the ADCS-CGIC: Figure 8 is a histogram of the distribution of patients’ scores on the ADCS-CGIC (Alzheimer’s Disease Cooperative Study—Clinicians Global Impression of Change) at 24 weeks. The mean difference in change scores between the Rivastigmine Tartrate Capsules and placebo groups from baseline was 0.5 points. This difference was statistically significant in favor of Rivastigmine Tartrate Capsules treatment.

Figure 8: Distribution of ADCS-CGIC Scores for Patients Completing 24 Weeks Of Treatment



Age, Gender and Race: Patients' age, gender, or race did not predict clinical outcome of Rivastigmine Tartrate Capsules treatment.

Pharmacokinetics

Rivastigmine is well absorbed with absolute bioavailability of about 40% (3 mg dose). It shows linear pharmacokinetics up to 3 mg BID but is non-linear at higher doses. Doubling the dose from 3 to 6 mg BID results in a 3-fold increase in AUC. The elimination half-life is about 1.5 hours, with most elimination as metabolites via the urine.

Absorption: Rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. Absolute bioavailability after a 3 mg dose is about 36%. Administration of Rivastigmine Tartrate Capsules with food delays absorption (t_{max}) by 90 minutes, lowers C_{max} by approximately 30% and increases AUC by approximately 30%.

Distribution: Rivastigmine is widely distributed throughout the body with a volume of distribution in the range of 1.8 to 2.7 L/kg. Rivastigmine penetrates the blood brain barrier, reaching CSF peak concentrations in 1.4 to 2.6 hours. Mean AUC_{1-12hr} ratio of CSF/plasma averaged $40 \pm 0.5\%$ following 1 to 6 mg BID doses.

Rivastigmine is about 40% bound to plasma proteins at concentrations of 1 to 400 ng/mL, which cover the therapeutic concentration range. Rivastigmine distributes equally between blood and plasma with a blood-to-plasma partition ratio of 0.9 at concentrations ranging from 1 to 400 ng/mL.

Metabolism: Rivastigmine is rapidly and extensively metabolized, primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. Based on evidence from *in vitro* and animal studies, the major cytochrome P450 isozymes are minimally involved in rivastigmine metabolism. Consistent with these observations is the finding that no drug interactions related to cytochrome P450 have been observed in humans [see Drug-Drug Interactions].

Elimination: The major pathway of elimination is via the kidneys. Following administration of ^{14}C -rivastigmine to 6 healthy volunteers total recovery of radioactivity over 120 hours was 97% in urine and 0.4% in feces. No parent drug was detected in urine. The sulfate conjugate of the decarbamylated metabolite is the major component excreted in urine and represents 40% of the dose. Mean oral clearance of rivastigmine is 1.8 ± 0.6 L/min after 6 mg BID.

Special Populations

Hepatic Disease: Following a single 3 mg dose, mean oral clearance of rivastigmine was 60% lower in hepatically impaired patients (n=10, biopsy proven) than in healthy subjects (n=10). After multiple 6 mg BID oral dosing, the mean clearance of rivastigmine was 65% lower in mild (n=7, Child-Pugh score 5 to 6) and moderate (n=3, Child-Pugh score 7 to 9) hepatically impaired patients (biopsy proven, liver cirrhosis) than in healthy subjects (n=10). Dosage adjustment is not necessary in hepatically impaired patients as the dose of drug is individually titrated to tolerability.

Renal Disease: Following a single 3 mg dose, mean oral clearance of rivastigmine is 64% lower in moderately impaired renal patients (n=8, GFR=10 to 50 mL/min) than in healthy subjects (n=10, GFR \geq 60 mL/min); Cl/F=1.7 L/min (cv=45%) and 4.8 L/min (cv=80%), respectively. In severely impaired renal patients (n=8, GFR<10mL/min), mean oral clearance of rivastigmine is 43% higher than in healthy subjects (n=10, GFR \geq 60 mL/min); Cl/F = 6.9 L/min and 4.8 L/min, respectively. For unexplained reasons, the severely impaired renal patients had a higher clearance of rivastigmine than moderately impaired patients. However, dosage adjustment may not be necessary in renally impaired patients as the dose of the drug is individually titrated to tolerability.

Age: Following a single 2.5 mg oral dose to elderly volunteers (>60 years of age, n=24) and younger volunteers (n=24), mean oral clearance of rivastigmine was 30% lower in elderly (7 L/min) than in younger subjects (10 L/min).

Gender and Race: No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of Rivastigmine Tartrate Capsules, but a population pharmacokinetic analysis indicates that gender (n=277 males and 348 females) and race (n=575 White, 34 Black, 4 Asian, and 12 Other) did not affect the clearance of Rivastigmine Tartrate capsules

Nicotine Use: Population PK analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% (n=75 Smokers and 549 Nonsmokers).

Drug-Drug Interactions

Effect of Rivastigmine Tartrate Capsules on the Metabolism of Other Drugs: Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of Rivastigmine Tartrate Capsules.

Effect of Other Drugs on the Metabolism of Rivastigmine Tartrate Capsules: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), β -blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15). In addition, in clinical trials, no increased risk of clinically relevant untoward

effects was observed in patients treated concomitantly with Rivastigmine Tartrate Capsules and these agents.

INDICATIONS AND USAGE

Rivastigmine Tartrate Capsule is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

Rivastigmine Tartrate Capsule is indicated for the treatment of mild to moderate dementia associated with Parkinson's disease.

The dementia of Parkinson's disease is purportedly characterized by impairments in executive function, memory retrieval, and attention, in patients with an established diagnosis of Parkinson's disease. The diagnosis of the dementia of Parkinson's disease, however, can reliably be made in patients in whom a progressive dementia syndrome occurs (without the necessity to document the specific deficits described above) at least 2 years after a diagnosis of Parkinson's disease has been made, and in whom other causes of dementia have been ruled out (see CLINICAL PHARMACOLOGY, Clinical Trial Data).

CONTRAINDICATIONS

Rivastigmine Tartrate Capsule is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation (see DESCRIPTION).

WARNINGS

GI Gastrointestinal Adverse Reactions

Rivastigmine Tartrate Capsules use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. For this reason, patients should always be started at a dose of 1.5 mg BID and titrated to their maintenance dose. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose (see DOSAGE AND ADMINISTRATION) to reduce the possibility of severe vomiting and its potentially serious sequelae (e.g., there has been one postmarketing report of severe vomiting with esophageal rupture following inappropriate reinitiation of treatment with a 4.5 mg dose after 8 weeks of treatment interruption.)

***Nausea and Vomiting:* In the controlled clinical trials, 47% of the patients treated with Rivastigmine Tartrate Capsules dose in the therapeutic range of 6 to 12 mg/day (n=1189) developed nausea (compared with 12% in placebo). A total of 31% of Rivastigmine Tartrate Capsules -treated patients developed at least one episode of vomiting (compared with 6% for placebo). The rate of vomiting was higher during the titration phase (24% vs. 3% for placebo) than in the maintenance phase (14% vs. 3% for placebo). The rates were higher in women than men. Five percent of patients discontinued for vomiting, compared to less than 1% for patients on placebo. Vomiting was severe in 2% of Rivastigmine Tartrate Capsules -treated patients and was rated as mild or moderate each in 14% of patients. The rate of nausea was higher during the titration phase (43% vs. 9% for placebo) than in the maintenance phase (17% vs. 4% for placebo).**

***Weight Loss:* In the controlled trials, approximately 26% of women on high doses of Rivastigmine Tartrate Capsules (greater than 9 mg/day) had weight loss equal to or greater than 7% of their**

baseline weight compared to 6% in the placebo-treated patients. About 18% of the males in the high dose group experienced a similar degree of weight loss compared to 4% in placebo-treated patients. It is not clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.

Anorexia: In the controlled clinical trials, of the patients treated with a Rivastigmine Tartrate Capsules dose of 6 to 12 mg/day, 17% developed anorexia compared to 3% of the placebo patients. Neither the time course nor the severity of the anorexia is known.

Peptic Ulcers/Gastrointestinal Bleeding: Because of their pharmacological action, cholinesterase inhibitors 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 at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). Clinical studies of Rivastigmine Tartrate Capsules have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Anesthesia

Rivastigmine Tartrate as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiovascular Conditions

Drugs that increase cholinergic activity may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with “sick sinus syndrome” or other supraventricular cardiac conduction conditions. In clinical trials, Rivastigmine Tartrate Capsules was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities. Syncopal episodes have been reported in 3% of patients receiving 6 to 12 mg/day of Rivastigmine Tartrate Capsules, compared to 2% of placebo patients.

Genitourinary

Although this was not observed in clinical trials of Rivastigmine Tartrate Capsules, drugs that increase cholinergic activity may cause urinary obstruction.

Neurological Conditions

Seizures: Drugs that increase cholinergic activity are believed to have some potential for causing seizures. However, seizure activity also may be a manifestation of Alzheimer’s Disease.

Pulmonary Conditions

Like other drugs that increase cholinergic activity, Rivastigmine Tartrate Capsules should be used with care in patients with a history of asthma or obstructive pulmonary disease.

PRECAUTIONS

Information for Patients and Caregivers

Caregivers should be advised of the high incidence of nausea and vomiting associated with the use of the drug along with the possibility of anorexia and weight loss. Caregivers should be encouraged to monitor for these adverse events and inform the physician if they occur. It is critical to inform

caregivers that if therapy has been interrupted for more than several days, the next dose should not be administered until they have discussed this with the physician.

Caregivers and patients should be advised that, like other cholinomimetics, Rivastigmine Tartrate Capsules may exacerbate or induce extrapyramidal symptoms. Worsening in patients with Parkinson's disease, including an increased incidence or intensity of tremor, has been observed.

Drug-Drug Interactions

Effect of Rivastigmine Tartrate Capsules on the Metabolism of Other Drugs: Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of Rivastigmine Tartrate Capsules.

Effect of Other Drugs on the Metabolism of Rivastigmine Tartrate Capsules: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), β -blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15).

Use with Anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In carcinogenicity studies conducted at dose levels up to 1.1 mg-base/kg/day in rats and 1.6 mg-base/kg/day in mice, rivastigmine was not carcinogenic. These dose levels are approximately 0.9 times and 0.7 times the maximum recommended human daily dose of 12 mg/day on a mg/m² basis.

Rivastigmine was clastogenic in two *in vitro* assays in the presence, but not the absence, of metabolic activation. It caused structural chromosomal aberrations in V79 Chinese hamster lung cells and both structural and numerical (polyploidy) chromosomal aberrations in human peripheral blood lymphocytes. Rivastigmine was not genotoxic in three *in vitro* assays: the Ames test, the unscheduled DNA synthesis (UDS) test in rat hepatocytes (a test for induction of DNA repair synthesis), and the HGPRT test in V79 Chinese hamster cells. Rivastigmine was not clastogenic in the *in vivo* mouse micronucleus test.

Rivastigmine had no effect on fertility or reproductive performance in the rat at dose levels up to 1.1 mg-base/kg/day. This dose is approximately 0.9 times the maximum recommended human daily dose of 12 mg/day on a mg/m² basis.

Pregnancy

Pregnancy Category B: Reproduction studies conducted in pregnant rats at doses up to 2.3 mg-base/kg/day (approximately 2 times the maximum recommended human dose on a mg/m² basis) and in pregnant rabbits at doses up to 2.3 mg-base/kg/day (approximately 4 times the maximum recommended human dose on a mg/m² basis) revealed no evidence of teratogenicity. Studies in rats showed slightly decreased fetal/pup weights, usually at doses causing some maternal toxicity; decreased weights were seen at doses which were several fold lower than the maximum recommended human dose on a mg/m² basis. There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Rivastigmine Tartrate Capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether rivastigmine is excreted in human breast milk. Rivastigmine Tartrate Capsule has no indication for use in nursing mothers.

Pediatric Use

There are no adequate and well-controlled trials documenting the safety and efficacy of Rivastigmine Tartrate Capsules in any illness occurring in children.

ADVERSE REACTIONS

Dementia of the Alzheimer's type

Adverse Events Leading to Discontinuation

The rate of discontinuation due to adverse events in controlled clinical trials of Rivastigmine Tartrate Capsules was 15% for patients receiving 6 to 12 mg/day compared to 5% for patients on placebo during forced weekly dose titration. While on a maintenance dose, the rates were 6% for patients on Rivastigmine Tartrate Capsules compared to 4% for those on placebo.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Clinical Trials during Titration and Maintenance in Patients Receiving 6 to 12 mg/day Rivastigmine Tartrate Capsules Using a Forced Dose Titration

Study Phase	Titration		Maintenance		Overall	
	Placebo (n=868)	Rivastigmine Tartrate Capsules ≥6 to 12 mg/day (n=1189)	Placebo (n=788)	Rivastigmine Tartrate Capsules ≥6 to 12 mg/day (n=987)	Placebo (n=868)	Rivastigmine Tartrate Capsules ≥6 to 12 mg/day (n=1189)
Event/ Discontinuing						
Nausea	<1	8	<1	1	1	8
Vomiting	<1	4	<1	1	<1	5
Anorexia	0	2	<1	1	<1	3
Dizziness	<1	2	<1	1	<1	2

Most Frequent Adverse Clinical Events Seen in Association with the Use of Rivastigmine Tartrate Capsules

The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are largely predicted by Rivastigmine Tartrate Capsules' cholinergic effects. These include nausea, vomiting, anorexia, dyspepsia, and asthenia.

Gastrointestinal Adverse Reactions

Rivastigmine Tartrate Capsules' use is associated with significant nausea, vomiting, and weight loss (see WARNINGS).

Adverse Events Reported in Controlled Trials

Table 2 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials and for which the rate of occurrence was greater for patients treated with Rivastigmine Tartrate Capsules doses of 6 to 12 mg/day than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

In general, adverse reactions were less frequent later in the course of treatment.

No systematic effect of race or age could be determined from the incidence of adverse events in the controlled studies. Nausea, vomiting and weight loss were more frequent in women than men.

Table 2. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Rivastigmine Tartrate Capsules (6 to 12 mg/day) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=868)	Rivastigmine Tartrate Capsules (6 to 12 mg/day) (n=1189)
Percent of Patients with any Adverse Event	79	92
Autonomic Nervous System		
Sweating increased	1	4
Syncope	2	3
Body as a Whole		
Accidental Trauma	9	10
Fatigue	5	9
Asthenia	2	6
Malaise	2	5
Influenza-like Symptoms	2	3
Weight Decrease	<1	3
Cardiovascular Disorders, General		
Hypertension	2	3
Central and Peripheral Nervous System		
Dizziness	11	21
Headache	12	17
Somnolence	3	5
Tremor	1	4
Gastrointestinal System		

Nausea	12	47
Vomiting	6	31
Diarrhea	11	19
Anorexia	3	17
Abdominal Pain	6	13
Dyspepsia	4	9
Constipation	4	5
Flatulence	2	4
Eructation	1	2
Psychiatric Disorders		
Insomnia	7	9
Confusion	7	8
Depression	4	6
Anxiety	3	5
Hallucination	3	4
Aggressive Reaction	2	3
Resistance Mechanism Disorders		
Urinary Tract Infection	6	7
Respiratory System		
Rhinitis	3	4

Other adverse events observed at a rate of 2% or more on Rivastigmine Tartrate Capsules 6 to 12 mg/day but at a greater or equal rate on placebo were chest pain, peripheral edema, vertigo, back pain, arthralgia, pain, bone fracture, agitation, nervousness, delusion, paranoid reaction, upper respiratory tract infection, infection (general), coughing, pharyngitis, bronchitis, rash (general), urinary incontinence.

Dementia Associated with Parkinson's disease

Adverse Events leading to discontinuation

The rate of discontinuation due to adverse events in the single controlled trial of Rivastigmine Tartrate Capsules was 18.2% for patients receiving 3 to 12 mg/day compared to 11.2% for patients on placebo during the 24 week study. The most frequent adverse events that led to discontinuation from this study, defined as those occurring in at least 1% of patients receiving Rivastigmine Tartrate Capsules and more frequent than those receiving placebo, were nausea (3.6% Rivastigmine Tartrate Capsules vs. 0.6% placebo), vomiting (1.9% Rivastigmine Tartrate Capsules vs 0.6% placebo), and tremor (1.7% Rivastigmine Tartrate Capsules vs. 0% placebo).

Most Frequent Adverse Clinical Events Seen in Association with the Use of Rivastigmine Tartrate Capsules

The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are largely predicted by Rivastigmine Tartrate Capsules' cholinergic effects. These include nausea, vomiting, tremor, anorexia, and dizziness.

Adverse Events Reported in Controlled Trials

Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials and for which the rate of occurrence was greater for patients treated with Rivastigmine Tartrate Capsules doses of 3 to 12 mg/day than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from

those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

In general, adverse reactions were less frequent later in the course of treatment.

Table 3. Adverse Events Reported in the Single Controlled Clinical Trial in at Least 2% of Patients Receiving Rivastigmine Tartrate Capsules (3 to 12 mg/day) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=179)	Rivastigmine Tartrate Capsules (3 to 12 mg/day) (n=362)
Percent of Patients with any Adverse Event	71	84
Gas trointestinal disorders		
Nausea	11	29
Vomiting	2	17
Diarrhea	4	7
Upper abdominal pain	1	4
General Disorders and administrative site conditions		
Fatigue	3	4
Asthenia	1	2
Metabolism and nutritional disorders		
Anorexia	3	6
Dehydration	1	2
Nervous system Disorders		
Tremor	4	10
Dizziness	1	6
Headache	3	4
Somnolence	3	4
Parkinson's disease (worsening)	1	3
Parkinsonism	1	2
Psychiatric Disorders		
Anxiety	1	4
Insomnia	2	3

Other Adverse Events Observed During Clinical Trials

Dementia of the Alzheimer's Type

Rivastigmine Tartrate Capsule has been administered to over 5297 individuals during clinical trials worldwide. Of these, 4326 patients have been treated for at least 3 months, 3407 patients have been treated for at least 6 months, 2150 patients have been treated for 1 year, 1250 have been treated for 2 years, and 168 have been treated for over 3 years. With regard to exposure to the highest dose, 2809 patients were exposed to doses of 10 to 12 mg, 2615 patients treated for 3 months, 2328 patients treated for 6 months, 1378 patients treated for 1 year, 917 patients treated for 2 years, and 129 treated for over 3 years.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 9 open-

label trials in North America, Western Europe, Australia, South Africa, and Japan were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified WHO dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 5297 patients from these trials who experienced that event while receiving Rivastigmine Tartrate Capsules. All adverse events occurring in at least 6 patients (approximately 0.1%) are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, relatively minor events, 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. These adverse events are not necessarily related to Rivastigmine Tartrate Capsules treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System: *Infrequent:* Cold clammy skin, dry mouth, flushing, increased saliva.

Body as a Whole: *Frequent:* Accidental trauma, fever, edema, allergy, hot flushes, rigors. *Infrequent:* Edema periorbital or facial, hypothermia, edema, feeling cold, halitosis.

Cardiovascular System: *Frequent:* Hypotension, postural hypotension, cardiac failure.

Central and Peripheral Nervous System: *Frequent:* Abnormal gait, ataxia, paresthesia, convulsions. *Infrequent:* Paresis, apraxia, aphasia, dysphonia, hyperkinesia, hyperreflexia, hypertonia, hypoesthesia, hypokinesia, migraine, neuralgia, nystagmus, peripheral neuropathy.

Endocrine System: *Infrequent:* Goiter, hypothyroidism.

Gastrointestinal System: *Frequent:* Fecal incontinence, gastritis. *Infrequent:* Dysphagia, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, GI hemorrhage, hernia, intestinal obstruction, melena, rectal hemorrhage, gastroenteritis, ulcerative stomatitis, duodenal ulcer, hematemesis, gingivitis, tenesmus, pancreatitis, colitis, glossitis.

Hearing and Vestibular Disorders: *Frequent:* Tinnitus.

Heart Rate and Rhythm Disorders: *Frequent:* Atrial fibrillation, bradycardia, palpitation. *Infrequent:* AV block, bundle branch block, sick sinus syndrome, cardiac arrest, supraventricular tachycardia, extrasystoles, tachycardia.

Liver and Biliary System Disorders: *Infrequent:* Abnormal hepatic function, cholecystitis.

Metabolic and Nutritional Disorders: *Frequent:* Dehydration, hypokalemia. *Infrequent:* Diabetes mellitus, gout, hypercholesterolemia, hyperlipemia, hypoglycemia, cachexia, thirst, hyperglycemia, hyponatremia.

Musculoskeletal Disorders: *Frequent:* Arthritis, leg cramps, myalgia. *Infrequent:* Cramps, hernia, muscle weakness.

Myo-, Endo-, Pericardial and Valve Disorders: *Frequent:* Angina pectoris, myocardial infarction.

Platelet, Bleeding, and Clotting Disorders: *Frequent:* Epistaxis. *Infrequent:* Hematoma, thrombocytopenia, purpura.

Psychiatric Disorders: *Frequent:* Paranoid reaction, confusion. *Infrequent:* Abnormal dreaming, amnesia, apathy, delirium, dementia, depersonalization, emotional lability, impaired concentration, decreased libido, personality disorder, suicide attempt, increased libido, neurosis, suicidal ideation, psychosis.

Red Blood Cell Disorders: *Frequent:* Anemia. *Infrequent:* Hypochromic anemia.

Reproductive Disorders (Female & Male): *Infrequent:* Breast pain, impotence, atrophic vaginitis.

Resistance Mechanism Disorders: *Infrequent:* Cellulitis, cystitis, herpes simplex, otitis media.

Respiratory System: *Infrequent:* Bronchospasm, laryngitis, apnea.

Skin and Appendages: *Frequent:* Rashes of various kinds (maculopapular, eczema, bullous, exfoliative, psoriaform, erythematous). *Infrequent:* Alopecia, skin ulceration, urticaria, contact dermatitis.

Special Senses: *Infrequent:* Perversion of taste, loss of taste.

Urinary System Disorders: *Frequent:* Hematuria. *Infrequent:* Albuminuria, oliguria, acute renal failure, dysuria, micturition urgency, nocturia, polyuria, renal calculus, urinary retention.

Vascular (extracardiac) Disorders: *Infrequent:* Hemorrhoids, peripheral ischemia, pulmonary embolism, thrombosis, deep thrombophlebitis, aneurysm, intracranial hemorrhage.

Vision Disorders: *Frequent:* Cataract. *Infrequent:* Conjunctival hemorrhage, blepharitis, diplopia, eye pain, glaucoma.

White Cell and Resistance Disorders: *Infrequent:* Lymphadenopathy, leukocytosis.

Dementia Associated with Parkinson's Disease

Rivastigmine Tartrate Capsules have been administered to 485 individuals during clinical trials worldwide. Of these, 413 patients have been treated for at least 3 months, 253 patients have been treated for at least 6 months, and 113 patients have been treated for 1 year.

Additional treatment emergent adverse events in patients with Parkinson's disease dementia occurring in at least 1 patient (approximately 0.3%) are listed below, excluding events that are already listed above for the dementia of the Alzheimer's type or elsewhere in labeling, WHO terms too general to be informative, relatively minor events, 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 1/1,000 patients. These adverse events are not necessarily related to Rivastigmine Tartrate Capsules treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Cardiovascular System: *Frequent:* Chest pain. *Infrequent:* Sudden cardiac death.

Central and Peripheral Nervous System: *Frequent:* Dyskinesia, bradykinesia, restlessness, transient ischemic attack. *Infrequent:* Dystonia, hemiparesis, epilepsy, restless leg syndrome.

Endocrine System: *Infrequent:* Elevated prolactin level.

Gastrointestinal System: *Frequent:* Dyspepsia. *Infrequent:* Fecaloma, dysphagia, diverticulitis,

peritonitis.

Hearing and Vestibular Disorders: *Frequent:* Vertigo. *Infrequent:* Meniere's disease.

Heart Rate and Rhythm Disorders: *Infrequent:* Adam-Stokes syndrome.

Liver and Biliary System Disorders: *Infrequent:* Elevated alkaline phosphatase level, elevated gamma-glutamyltransferase level.

Musculoskeletal Disorders: *Frequent:* Back pain. *Infrequent:* Muscle stiffness, myoclonus, freezing phenomenon.

Psychiatric Disorders: *Frequent:* Agitation, depression. *Infrequent:* Delusion, insomnia.

Reproductive Disorders (Female & Male): *Infrequent:* endometrial hypertrophy, mastitis, prostatic adenoma.

Respiratory System: *Frequent:* Dyspnoea. *Infrequent:* Cough

Urinary System Disorders: *Infrequent:* Urinary incontinence, neurogenic bladder.

Vascular (extracardiac) Disorders: *Infrequent:* Vasovagal syncope, vasculitis.

Vision Disorders: *Infrequent:* Blurred vision, blepharospasm, conjunctivitis, retinopathy.

Post-Introduction Reports

Voluntary reports of adverse events temporally associated with Rivastigmine Tartrate Capsules that have been received since market introduction that are not listed above, and that may or may not be causally related to the drug include the following:

Skin and Appendages: Stevens-Johnson syndrome.

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 Rivastigmine Tartrate Capsule has a short plasma half-life of about one hour and a moderate duration of acetylcholinesterase inhibition of 8 to 10 hours, it is recommended that in cases of asymptomatic overdoses, no further dose of Rivastigmine Tartrate Capsules should be administered for the next 24 hours.

As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Atypical responses in blood pressure and heart rate have been reported with other drugs that increase cholinergic activity when co-administered with quaternary anticholinergics such as glycopyrrolate. Due to the short half-life of Rivastigmine Tartrate Capsules, dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) would not be clinically indicated in the event of an overdose.

In overdoses accompanied by severe nausea and vomiting, the use of antiemetics should be considered. In a documented case of a 46 mg overdose with Rivastigmine Tartrate Capsules, the patient experienced

vomiting, incontinence, hypertension, psychomotor retardation, and loss of consciousness. The patient fully recovered within 24 hours and conservative management was all that was required for treatment.

DOSAGE AND ADMINISTRATION

Dementia of the Alzheimer's type

The dosage of Rivastigmine Tartrate Capsules shown to be effective in controlled clinical trials in Alzheimer's Disease is 6 to 12 mg/day, given as twice a day dosing (daily doses of 3 to 6 mg BID). There is evidence from the clinical trials that doses at the higher end of this range may be more beneficial.

The starting dose of Rivastigmine Tartrate Capsules is 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of 2 weeks of treatment, the dose may be increased to 3 mg BID. Subsequent increases to 4.5 mg BID and 6 mg BID should be attempted after a minimum of 2 weeks at the previous dose. If adverse effects (e.g., nausea, vomiting, abdominal pain, loss of appetite) cause intolerance during treatment, the patient should be instructed to discontinue treatment for several doses and then restart at the same or next lower dose level. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose and titrated as described above (see WARNINGS). The maximum dose is 6 mg BID (12 mg/day).

Dementia associated with Parkinson's Disease

The dosage of Rivastigmine Tartrate Capsules shown to be effective in the single controlled clinical trial conducted in dementia associated with Parkinson's Disease is 3 to 12 mg/day, given as twice-a-day dosing (daily doses of 1.5 to 6 mg BID). In that medical condition, the starting dose of Rivastigmine Tartrate Capsules is 1.5 mg BID; subsequently, the dose may be increased to 3 mg BID and further to 4.5 mg BID and 6 mg BID, based on tolerability, with a minimum of 4 weeks at each dose.

Rivastigmine Tartrate Capsules should be taken with meals in divided doses in the morning and evening.

HOW SUPPLIED

Rivastigmine Tartrate Capsules equivalent to 6 mg of rivastigmine base are available as follows:

6 mg Capsule – orange, "148" is printed in black on the body and cap of the capsule.

Bottles of 60's with Child Resistant Cap	NDC 54868- 6145-0
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Storage: Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Dispense in a tight container.

Distributed by:

Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

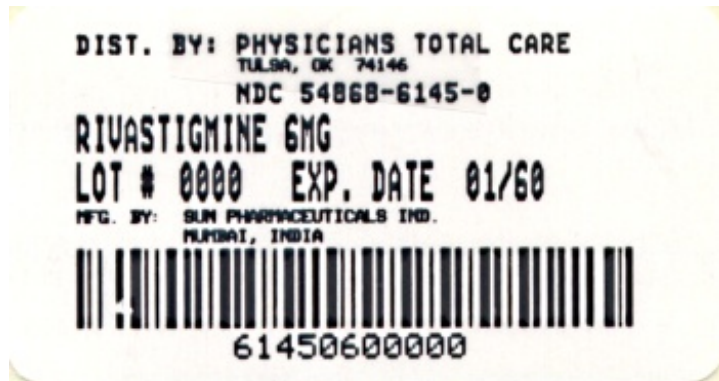
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Relabeling of "Additional Barcode Label" by:
Physicians Total Care, Inc.
Tulsa, OK 74146

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL-Bottle Label-6 mg

Rivastigmine Tartrate Capsules
equivalent to 6 mg base
Rx only
60 CAPSULES



RIVASTIGMINE TARTRATE

rivastigmine tartrate capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54868-6145(NDC:62756-148-86)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RIVASTIGMINE TARTRATE (UNII: 9IY2357JPE) (RIVASTIGMINE - UNII:PKI06M3IW0)	RIVASTIGMINE TARTRATE	6 mg

Inactive Ingredients	
Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

Product Characteristics

Color	orange (orange opaque)	Score	no score
Shape	CAPSULE	Size	18mm
Flavor		Imprint Code	148;148
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-6145-0	60 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077131	09/15/2010	

Labeler - Physicians Total Care, Inc. (194123980)

Establishment

Name	Address	ID/FEI	Business Operations
Physicians Total Care, Inc.		194123980	relabel

Revised: 6/2010

Physicians Total Care, Inc.