

RIVASTIGMINE TARTRATE - rivastigmine tartrate capsule
Alembic Pharmaceuticals Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Rivastigmine Tartrate Capsules USP safely and effectively. See full prescribing information for Rivastigmine Tartrate Capsules USP.

Rivastigmine Tartrate Capsules USP, for oral use.

Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Dosage and Administration, Dosing in Specific Populations (2.2) 9/2013
Contraindications (4) 9/2013
Warnings and Precautions, Hypersensitivity Reactions of the Skin (5.2) 9/2013

INDICATIONS AND USAGE

Rivastigmine tartrate capsules, are an acetylcholinesterase inhibitor indicated for treatment of: (1)

- Mild to moderate dementia of the Alzheimer's type (1.1)
- Mild to moderate dementia associated with Parkinson's disease (1.2)

DOSAGE AND ADMINISTRATION

Alzheimer's Disease: (2)

- Initiate treatment with 1.5 mg twice a day
- After a minimum of 2 weeks, if tolerated, increase dose to 3 mg twice a day and further to 4.5 mg twice a day and 6 mg twice a day if tolerated with a minimum of 2 weeks at each dose (2.1)

Parkinson's Disease Dementia: (2)

- Initiate treatment with 1.5 mg twice a day
- After a minimum of 4 weeks, if tolerated, increase dose to 3 mg twice a day and further to 4.5 mg twice a day and 6 mg twice a day if tolerated with a minimum of 4 weeks at each dose (2.2)

Rivastigmine tartrate capsules should be taken with meals in divided doses in the morning and evening.

(2.1) Rivastigmine tartrate oral solution and Rivastigmine tartrate capsules may be interchanged at equal doses. (2.3) (2)

DOSAGE FORMS AND STRENGTHS

- Capsules: 1.5 mg, 3 mg, 4.5 mg and 6 mg (3.1).

CONTRAINDICATIONS

- Known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation (4)
- History of application site reaction with rivastigmine transdermal patch suggestive of allergic contact dermatitis, in the absence of negative allergy testing (4, 5.2)

WARNINGS AND PRECAUTIONS

- Gastrointestinal adverse reactions: may include significant nausea, vomiting, diarrhea, anorexia/decreased appetite, and weight loss, and may necessitate treatment interruption. Dehydration may result from prolonged vomiting or diarrhea and can be associated with serious outcomes. (5.1)
- Hypersensitivity reactions of the skin: Discontinue rivastigmine in case of disseminated hypersensitivity reaction of the skin, which may occur after oral or transdermal administration. (4, 5.2) In patients with suspected allergic contact dermatitis after transdermal rivastigmine use, switch to oral rivastigmine only after negative allergy testing.

ADVERSE REACTIONS

Most commonly observed adverse reactions (>5% and 2 times greater than placebo): nausea, vomiting, anorexia, dyspepsia, and asthenia. (6.1) (6)

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

DRUG INTERACTIONS

Cholinomimetic and anticholinergic drugs: Avoid concomitant use unless clinically necessary. (7.1) (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS & USAGE

1.1 Alzheimer's Disease

Rivastigmine tartrate capsules are indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

1.2 Parkinson's Disease Dementia

Rivastigmine tartrate capsules are indicated for the treatment of mild to moderate dementia associated with Parkinson's disease.

2 DOSAGE & ADMINISTRATION

2.1 Recommended Dosing

Rivastigmine tartrate capsules should be taken with meals in divided doses in the morning and evening.

Alzheimer's Disease

The dosage of Rivastigmine tartrate capsules shown to be effective in controlled clinical trials in Alzheimer's disease is 6 mg to 12 mg per day, administered twice a day (daily doses of 3 mg to 6 mg twice a day). There is evidence from the clinical trials that doses at the higher end of this range may be more beneficial.

Initial Dose

Initiate treatment with the 1.5 mg twice a day with Rivastigmine tartrate capsules.

Dose Titration

After a minimum of 2 weeks and if well tolerated, increase the dose to 3 mg twice a day. Subsequent increases to 4.5 mg twice a day and 6 mg twice a day should be attempted after a minimum of 2 weeks at the previous dose and if well tolerated. The maximum dose is 6 mg twice a day (12 mg per day).

Parkinson's Disease Dementia

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 mg to 12 mg per day, administered twice a day (daily doses of 1.5 mg to 6 mg twice a day).

Initial Dose

Initiate treatment with the 1.5 mg twice a day with Rivastigmine tartrate capsules.

Dose Titration

After a minimum of 4 weeks and if well tolerated, increase the dose to 3 mg twice a day. Subsequent increases to 4.5 mg twice a day and 6 mg twice a day should be attempted after a minimum of 4 weeks at the previous dose and if well tolerated. The maximum dose is 6 mg twice a day (12 mg per day).

Interruption of Treatment

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 dosing is interrupted for 3 days or fewer, restart treatment with the same or lower dose of Rivastigmine tartrate capsules. If dosing is interrupted for more than 3 days, treatment should be restarted with 1.5 mg twice a day and titrated as described above [see Warnings and Precautions (5.1)].

2.2 Dosing in Specific Populations

Dosing Modifications in Patients with Renal or Hepatic Impairment

Pharmacokinetic studies of oral rivastigmine in patients with moderate to severe renal impairment (glomerular filtration rate [GFR] <50 mL/min) and mild to moderate hepatic impairment (Child-Pugh score 5 to 9) showed reduced clearance of the drug [see Use in Specific Populations (8.6, 8.7), Clinical Pharmacology (12.3)]. Accordingly, such patients may be able to only tolerate lower doses. No data are available on the use of rivastigmine in patients with severe hepatic impairment.

Dosing Modifications in Patients with Low Body Weight

Because rivastigmine blood levels vary with body weight [see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)], careful titration and monitoring should be performed in patients with low body weight. In patients with low body weight (less than 50 kg), monitor closely for toxicities (e.g., excessive nausea, vomiting), and consider reducing the dose if such toxicities develop.

2.3 Important Administration Instructions

Rivastigmine tartrate oral solution and Rivastigmine tartrate capsules may be interchanged at equal doses.

3 DOSAGE FORMS & STRENGTHS

3.1 Rivastigmine Tartrate Capsules

Rivastigmine tartrate Capsules equivalent to 1.5 mg, 3 mg, 4.5 mg, or 6 mg of rivastigmine base are available as follows:

1.5 mg Capsule - pale yellow opaque / pale yellow opaque size "2" hard gelatin capsules radially imprinted with "B" on cap and "793" on body with black ink, filled with white to off-white free flowing powder.

3 mg Capsule - orange opaque / orange opaque size "2" hard gelatin capsules radially imprinted with "B" on cap and "794" on body with black ink, filled with white to off-white free flowing powder.

4.5 mg Capsule - coral red opaque / coral red opaque size "2" hard gelatin capsules radially imprinted with "B" on cap and "795" on body with black ink, filled with white to off-white free flowing powder.

6 mg Capsule - orange opaque / coral red opaque size "2" hard gelatin capsules radially imprinted with "B" on cap and "796" on body with black ink, filled with white to off-white free flowing powder.

4 CONTRAINDICATIONS

Rivastigmine tartrate capsules are contraindicated in patients with:

- known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation [see *Description (11)*].
- a previous history of application site reaction with rivastigmine transdermal patch suggestive of allergic contact dermatitis, in the absence of negative allergy testing [see *Warnings and Precautions (5.2)*].

Isolated cases of generalized skin reactions have been described in postmarketing experience [see *Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Adverse Reactions

Rivastigmine tartrate can cause gastrointestinal adverse reactions, including significant nausea, vomiting, diarrhea, anorexia/decreased appetite, and weight loss. Dehydration may result from prolonged vomiting or diarrhea and can be associated with serious outcomes. The incidence and severity of these reactions are dose-related [see *Adverse Reactions (6.1)*]. For this reason, patients should always be started at a dose of 1.5 mg twice a day and titrated to their maintenance dose.

If treatment is interrupted for longer than 3 days, treatment should be reinitiated with the lowest daily dose [see *Dosage and Administration (2.1)*] 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).

Inform caregivers to monitor for gastrointestinal adverse reactions and to inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than 3 days because of intolerance, the next dose should not be administered without contacting the physician regarding proper retitration.

5.2 Hypersensitivity Reactions of the Skin

There have been isolated postmarketing reports of patients experiencing disseminated hypersensitivity reactions of the skin when administered rivastigmine irrespective of the route of administration (oral or transdermal). Treatment should be discontinued if disseminated hypersensitivity reaction of the skin occurs [see *Contraindications (4)*]. Patients and caregivers should be instructed accordingly [see *Patient Counseling Information(17)*].

In patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine tartrate patch and who still require rivastigmine, treatment should be switched to oral rivastigmine only after negative allergy testing and under close medical supervision. It is possible that some patients sensitized to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

5.3 Other Adverse Reactions from Increased Cholinergic Activity

Neurologic Effects

Extrapyramidal Symptoms: Cholinomimetics, including rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening of parkinsonian symptoms, particularly tremor, has been observed in patients with dementia associated with Parkinson's disease who were treated with rivastigmine tartrate capsules.

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.

Peptic Ulcers/Gastrointestinal Bleeding

Cholinesterase inhibitors, including rivastigmine, may be expected to increase gastric acid secretion due to increased cholinergic activity. Monitor patients using Rivastigmine tartrate capsules 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 have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Use with Anesthesia

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

Cardiac Conduction Effects

Because rivastigmine increases cholinergic activity, use of rivastigmine may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important in patients with sick sinus syndrome or other supraventricular cardiac conduction conditions. In clinical trials, rivastigmine 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 mg to 12 mg per day of rivastigmine tartrate, compared to 2% of placebo patients.

Genitourinary Effects

Although not observed in clinical trials of rivastigmine, drugs that increase cholinergic activity may cause urinary obstruction.

Pulmonary Effects

Drugs that increase cholinergic activity, including rivastigmine, should be used with care in patients with a history of asthma or obstructive pulmonary disease.

5.4 Impairment in Driving or Use of Machinery

Dementia may cause gradual impairment of driving performance or compromise the ability to use machinery. The administration of rivastigmine may also result in adverse reactions that are detrimental to these functions. During treatment with rivastigmine tartrate capsules, routinely evaluate the patient's ability to continue driving or operating machinery.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in other sections of the prescribing information:

- Gastrointestinal Adverse Reactions [see *Warnings and Precautions (5.1)*].
- Hypersensitivity Reactions of the Skin [see *Warnings and Precautions (5.2)*].
- Other Adverse Reactions from Increased Cholinergic Activity [see *Warnings and Precautions (5.3)*].

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.

Rivastigmine tartrate has been administered to over 5,297 individuals during clinical trials worldwide. Of these, 4,326 patients have been treated for at least 3 months, 3,407 patients have been treated for at least 6 months, 2,150 patients have been treated for 1 year, 1,250 patients have been treated for 2 years, and 168 patients have been treated for over 3 years. With regard to exposure to the highest dose, 2,809 patients were exposed to doses of 10 mg to 12 mg, 2,615 patients treated for 3 months, 2,328 patients treated for 6 months, 1,378 patients treated for 1 year, 917 patients treated for 2 years, and 129 patients treated for over 3 years.

Mild to Moderate Alzheimer's Disease

Most Commonly Observed Adverse Reactions

The most common adverse reactions, defined as those occurring at a frequency of at

least 5% and twice the placebo rate, are largely predicted by rivastigmine tartrate's cholinergic effects. These include nausea, vomiting, anorexia, dyspepsia, and asthenia.

Gastrointestinal Adverse Reactions

Rivastigmine tartrate use is associated with significant nausea, vomiting, and weight loss [see Warnings and Precautions (5.1)].

Discontinuation Rates

The rate of discontinuation due to adverse events in controlled clinical trials of rivastigmine tartrate was 15% for patients receiving 6 mg to 12 mg per 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 compared to 4% for those on placebo.

The most common adverse reactions 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 Reactions Leading to Withdrawal from Clinical Trials during Titration and Maintenance in Patients Receiving 6 mg to 12 mg per day Rivastigmine Tartrate Using a Forced-Dose Titration

Study Phase	Titration		Maintenance		Overall	
	Rivastigmine tartrate ≥ 6 to 12 mg/day (n=1,189)	Placebo (n=868)	Rivastigmine tartrate ≥ 6 to 12 mg/day (n=987)	Placebo (n=788)	Rivastigmine tartrate ≥ 6 to 12 mg/day (n=1,189)	Placebo (n=868)
Event/% Discontinuing						
Nausea	8	< 1	1	< 1	8	1
Vomiting	4	< 1	1	< 1	5	< 1
Anorexia	2	0	1	< 1	3	< 1
Dizziness	2	< 1	1	< 1	2	< 1

Adverse Reactions Observed at an Incidence of at Least 2%

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 doses of 6 mg to 12 mg per 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 nondrug 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 Proportion of Adverse Reactions Observed with a Frequency of $\geq 2\%$ and at a Rate Greater than Placebo in Clinical Trials

Body System/Adverse Reaction	Rivastigmine Tartrate (6 to 12 mg/day) (n=1,189)	Placebo (n=868)
Percent of Patients with any Adverse Event	92	79
Autonomic Nervous System		

Sweating Increased	4	1
Syncope	3	2
Body as a Whole		
Fatigue	9	5
Asthenia	6	2
Malaise	5	2
Weight Decrease**	3	<1
Cardiovascular Disorders, General		
Hypertension	3	2
Central and Peripheral Nervous System		
Dizziness	21	11
Headache	17	12
Somnolence	5	3
Tremor	4	1
Gastrointestinal System		
Nausea*	47	12
Vomiting*	31	6
Diarrhea	19	11
Anorexia***	17	3
Abdominal Pain	13	6
Dyspepsia	9	4
Psychiatric Disorders		
Insomnia	9	7
Confusion	8	7
Depression	6	4
Anxiety	5	3
Hallucination	4	3
Aggressive Reaction	3	2
Resistance Mechanism Disorders		
Urinary Tract Infection	7	6

*Nausea and Vomiting: In the controlled clinical trials, 47% of the patients treated with a rivastigmine tartrate dose in the therapeutic range of 6 mg to 12 mg per day (n=1189) developed nausea (compared with 12% in placebo). A total of 31% of rivastigmine tartrate -treated patients developed at least 1 episode of vomiting (compared with 6% for placebo). The rate of vomiting was higher during the titration phase (24% versus 3% for placebo) than in the maintenance phase (14% versus 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-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% versus 9% for placebo) than in the maintenance phase (17% versus 4% for placebo).

**Weight Decreased: In the controlled trials, approximately 26% of women on high doses of rivastigmine tartrate (greater than 9 mg per 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 dose of 6 mg to 12 mg per day, 17% developed anorexia compared to 3% of the placebo patients. Neither the time course nor the severity of the anorexia is known.

Mild to Moderate Parkinson's Disease Dementia

Rivastigmine tartrate has been administered to 779 individuals during clinical trials worldwide. Of these, 663 patients have been treated for at least 3 months, 476 patients have been treated for at least 6 months, and 313 patients have been treated for 1 year.

Most Commonly Observed Adverse Reactions

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's cholinergic effects. These include nausea, vomiting, tremor, anorexia, and dizziness.

Discontinuation Rates

The rate of discontinuation due to adverse events in the single placebo-controlled trial of rivastigmine tartrate was 18.2% for patients receiving 3 mg to 12 mg per 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 and more frequent than those receiving placebo, were nausea (3.6% rivastigmine tartrate versus 0.6% placebo), vomiting (1.9% rivastigmine tartrate versus 0.6% placebo), and tremor (1.7% rivastigmine tartrate versus 0.0% placebo).

Adverse Reactions Observed at an Incidence of at Least 2%

Table 3 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in a single placebo-controlled trial and during the first 24 weeks of a 76-week open-label active-controlled trial for which the rate of occurrence was greater for patients treated with rivastigmine tartrate doses of 3 mg to 12 mg per day than for those treated with placebo in the placebo-controlled trial. 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 1 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 Proportion of Adverse Reactions Observed at a Frequency $\geq 2\%$ and Occurring at Rate Greater than Placebo in Clinical Trials

Controlled Body System/Adverse Event	Active-	Placebo-Controlled Study	
	Rivastigmine tartrate (3 to 12 mg/day) (n=294)	Rivastigmine tartrate (3 to 12 mg/day) (n=362)	Placebo (n=179)
Percent of Patients with any Adverse Event	88	84	71
Gastrointestinal Disorders			
Nausea	38	29	11
Vomiting	13	17	2
Diarrhea	8	7	4
Upper Abdominal Pain	4	4	1
Salivary hypersecretion	2	1	0
General Disorders and Administrative Site Conditions			
Fall	10	6	6
Fatigue	5	4	3
Asthenia	4	2	1
Metabolism and Nutritional Disorders			
Anorexia	-	6	3
Decreased Appetite	5	8	5
Dehydration	1	2	1
Nervous System Disorders			
Tremor	23	10	4
Dizziness	8	6	1
Headache	4	4	3
Somnolence	6	4	3
Parkinson's Disease (worsening)	.*	3	1
Bradykinesia	3	3	2
Dyskinesia	3	1	1
Cogwheel rigidity	3	1	0
Hypokinesia	2	1	0
Parkinsonism	-	2	0
Psychiatric Disorders			
Anxiety	4	4	1
Insomnia	2	3	2
Restlessness	1	3	2
Skin and Subcutaneous Tissue Disorders			
Sweating increased	2	2	1

*Parkinson's disease (worsening) in the active-controlled study was assessed by reported pre-identified adverse events (tremor, cogwheel rigidity, fall), each of them listed with corresponding frequencies.

Other Adverse Events Observed During Clinical Trials

Mild to Moderate Alzheimer's Disease

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 5,297 patients from these trials who experienced that event while receiving rivastigmine tartrate. 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 1/1,000 patients. These adverse events are not necessarily related to rivastigmine tartrate treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System: *Infrequent*: Increased saliva.

Body as a Whole: *Frequent*: Allergy, hot flushes.

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

Central and Peripheral Nervous System: *Frequent*: Abnormal gait, ataxia, paresthesia, convulsions. *Infrequent*: Dysphonia, hypoesthesia, migraine, nystagmus.

Gastrointestinal System: *Frequent*: Gastritis, constipation, flatulence. *Infrequent*: Gastric ulcer, gastroesophageal reflux, GI hemorrhage, hernia, melena, rectal hemorrhage, duodenal ulcer, hematemesis, pancreatitis.

Hearing and Vestibular Disorders: *Frequent*: Tinnitus.

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

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

Metabolic and Nutritional Disorders: *Frequent*: Dehydration, hypokalemia. *Infrequent*: Hyponatremia.

Musculoskeletal Disorders: *Infrequent*: Muscle weakness.

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

Psychiatric Disorders: *Frequent*: Confusion. *Infrequent*: Apathy, suicide attempt, increased libido, suicidal ideation.

Reproductive Disorders (Female and Male): *Infrequent*: Breast pain.

Resistance Mechanism Disorders: *Infrequent*: Herpes simplex, otitis media. Respiratory System: *Infrequent*: Bronchospasm.

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

Urinary System Disorders: *Frequent*: Hematuria. *Infrequent*: Acute renal failure, dysuria.

Vascular (extracardiac) Disorders: *Infrequent*: Peripheral ischemia, intracranial hemorrhage. Vision Disorders: *Frequent*: Cataract. *Infrequent*: Diplopia, glaucoma.

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

Mild to Moderate Parkinson's Disease Dementia

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 treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Central and Peripheral Nervous System: *Frequent*: Transient ischemic attack.
Gastrointestinal System: *Frequent*: Dyspepsia. *Infrequent*: Fecaloma, dysphagia.

General Disorders and Administration Site Conditions: *Frequent*: Chest pain.

Liver and Biliary System Disorders: *Infrequent*: Elevated gamma-glutamyltransferase level. Musculoskeletal Disorders: *Frequent*: Back pain. *Infrequent*: Muscle stiffness.

Psychiatric Disorders: *Frequent*: Agitation, depression.

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

Urinary System Disorders: *Infrequent*: Urinary incontinence.

Vision Disorders: *Infrequent*: Blurred vision.

6.2 Postmarketing Experience

Voluntary reports of adverse events temporally associated with rivastigmine tartrate 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:

Hepatobiliary Disorders: Hepatitis.

Psychiatric Disorders: Aggression.

Skin and Appendages: Stevens-Johnson syndrome, disseminated cutaneous hypersensitivity reactions.

7 DRUG INTERACTIONS

7.1 Cholinomimetic and Anticholinergic Drugs

Increased cholinergic effects may be expected when rivastigmine is given with other cholinomimetic drugs. Rivastigmine may also interfere with the activity of anticholinergic medications. Avoid concomitant use of rivastigmine with drugs having these pharmacologic effects unless deemed clinically necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Reproduction studies conducted in pregnant rats and rabbits at oral doses up to 2.3 mg-base/kg/day, or 2 (rat) and 4 (rabbit) times the maximum recommended human dose (MRHD) of 12 mg/day on a mg/m² basis, revealed no evidence of teratogenicity. Studies in pregnant rats showed slightly decreased fetal/pup weight at doses that were below the MRHD but usually associated with some maternal toxicity. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Rivastigmine and its metabolites are excreted in rat milk following oral administration of rivastigmine; levels of rivastigmine plus metabolites in rat milk are approximately 2 times that in maternal plasma. It is not known whether rivastigmine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivastigmine tartrate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established and therefore the use of rivastigmine in children and adolescents (below 18 years of age) is not recommended.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of rivastigmine tartrate, 86 percent were 65 years and older while 46 percent were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

In patients with moderate to severe renal impairment (glomerular filtration rate [GFR] <50 mL/min), clearance of oral rivastigmine was reduced [see *Clinical Pharmacology (12.3)*]. Accordingly, such patients may be able to only tolerate lower doses.

8.7 Hepatic Impairment

In patients with mild or moderate hepatic impairment (Child-Pugh score 5 to 9), clearance of oral rivastigmine was reduced [see *Clinical Pharmacology (12.3)*]. Accordingly, such patients may be able to only tolerate lower doses. No data are available on the use of rivastigmine in patients with severe hepatic impairment.

8.8 Low or High Body Weight

Because rivastigmine blood levels vary with weight, careful titration and monitoring should be performed in patients with low or high body weights. Compared to a patient with a body weight of 65 kg, the rivastigmine steady-state concentrations in a patient with a body weight of 35 kg would be approximately doubled, while for a patient with a body weight of 100 kg the concentrations would be approximately halved. In patients with low body weight (<50 kg), monitor closely for toxicities (e.g., excessive nausea, vomiting), and consider reducing the dose of Rivastigmine tartrate capsules if such toxicities develop.

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 rivastigmine has a short plasma half-life of about 1 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 coadministered with quaternary anticholinergics such as glycopyrrolate. Due to the short half-life of rivastigmine, dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) would not be clinically indicated in the event of an overdose.

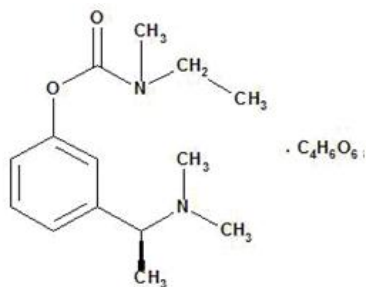
In overdoses accompanied by severe nausea and vomiting, the use of antiemetics should be considered. In a documented case of a 46 mg overdose with rivastigmine tartrate, the patient experienced vomiting, incontinence, hypertension, psychomotor retardation, and loss of consciousness. The patient fully recovered within 24 hours and conservative management was all that was required for treatment.

11 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 an empirical 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 3.0.



Rivastigmine Tartrate Capsules USP 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 hypromellose, magnesium stearate, microcrystalline cellulose, and colloidal silicon dioxide. Each hard-gelatin capsule contains gelatin, titanium dioxide and red and/or yellow iron oxides.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Although the precise mechanism of action of rivastigmine is unknown, it is thought 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. Therefore, the effect of rivastigmine 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.

12.2 Pharmacodynamics

After a 6-mg dose of rivastigmine, anticholinesterase activity is present in cerebrospinal fluid (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.

12.3 Pharmacokinetics

Rivastigmine shows linear pharmacokinetics up to 3 mg twice a day but is nonlinear at higher doses. Doubling the dose from 3 mg to 6 mg twice a day 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 with food delays absorption (t_{max}) by 90 minutes lowers C_{max} by approximately 30% and increases AUC by approximately 30%.

Distribution

Rivastigmine is weakly bound to plasma proteins (approximately 40%) over the therapeutic range. It readily crosses the blood-brain barrier, reaching CSF peak concentrations in 1.4 to 2.6 hours. It has an apparent volume of distribution in the range of 1.8 to 2.7 L/kg.

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 Interactions* (7.1)].

Elimination

The major pathway of elimination is via the kidneys. Following administration of ¹⁴C-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 twice a day.

Renal Impairment

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 and 4.8 L/min, respectively. In patients with severe renal impairment (n=8, GFR <10 mL/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. Despite this finding, such patients may be able to only tolerate lower doses.

Hepatic Impairment

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 twice a day 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). Accordingly, such patients may be able to only tolerate lower doses.

-

Body Weight

A relationship between drug exposure at steady-state (rivastigmine and metabolite NAP226-90) and body weight was observed in Alzheimer's dementia patients. Rivastigmine exposure is higher in subjects with low body weight. Compared to a patient with a body weight of 65 kg, the rivastigmine steady-state concentrations in a patient with a body weight of 35 kg would be approximately doubled, while for a patient with a body weight of 100 kg the concentrations would be approximately halved.

Age

Following a single 2.5-mg oral dose to elderly volunteers (60 years and older, 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 or Race

Population pharmacokinetic analysis of oral rivastigmine indicated that neither gender (n=277 males and 348 females) nor race (n=575 Caucasian, 34 Black, 4 Asian, and 12 Other) affected clearance of the drug.

Smoking

Population pharmacokinetic analysis showed that nicotine use increased the oral clearance of rivastigmine by 23% (n=75 smokers and 549 nonsmokers).

Drug Interaction Studies

Effect of Rivastigmine 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, CYP2C19, or CYP2B6.

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

Effect of Other Drugs on the Metabolism of Rivastigmine

Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine.

Population pharmacokinetic analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine taken orally 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), NSAIDs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35) and antihistamines (n=15).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis & Mutagenesis & Impairment Of Fertility

Carcinogenesis

In oral carcinogenicity studies conducted at doses up to 1.1 mg-base/kg/day in rats and 1.6 mg-base/kg/day in mice, rivastigmine was not carcinogenic. These doses are less than the maximum recommended human dose (MRHD) of 12 mg/day on a mg/m² basis.

Mutagenesis

Rivastigmine was clastogenic in *in vitro* chromosomal aberration assays in mammalian cells in the presence, but not the absence, of metabolic activation. Rivastigmine was negative in an *in vitro* bacterial reverse mutation (Ames) assay, an *in vitro* HGPRT assay, and in an *in vivo* mouse micronucleus test.

Impairment of Fertility

Rivastigmine had no effect on fertility or reproductive performance in rats at oral doses up to 1.1 mg-base/kg/day, a dose less than the MRHD on a mg/m² basis.

14 CLINICAL STUDIES

Mild to Moderate Alzheimer's Disease

The effectiveness of rivastigmine tartrate as a treatment for Alzheimer's disease is demonstrated by the results of 2 randomized, double-blind, placebo-controlled clinical investigations (*Study 1 and Study 2*) 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 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%.

In each study, the effectiveness of rivastigmine tartrate was evaluated using a dual outcome assessment strategy.

The ability of rivastigmine tartrate 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 trials was approximately 3 to 8 units per year.

The ability of rivastigmine tartrate 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 cannot be compared directly with the results of CIBIC-Plus evaluations from other clinical trials. The CIBIC-Plus used in the rivastigmine tartrate trials was a structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of 3 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 of Rivastigmine Tartrate in Mild to Moderate Alzheimer's Disease (Study 1)

In a study of 26 weeks duration, 699 patients were randomized to either a dose range of 1 mg to 4 mg or 6 mg to 12 mg of rivastigmine tartrate 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.

Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all 3 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-treated patients compared to the patients on placebo were 1.9 and 4.9 units for the 1 mg to 4 mg and 6 mg to 12 mg treatments, respectively. Both treatments were statistically significantly superior to placebo and the 6 mg to 12 mg per day range was significantly superior to the 1 mg to 4 mg per day range.

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

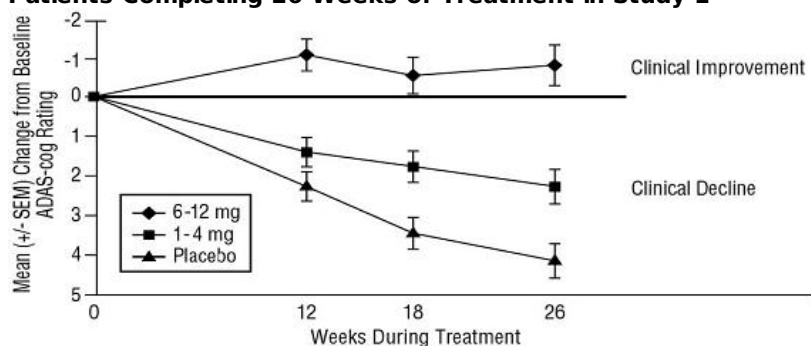


Figure 2 illustrates the cumulative percentages of patients from each of the 3 treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified for 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 and placebo have a wide range of responses, but that the rivastigmine tartrate 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 mg-4 mg 85%, and 6 mg-12 mg 65%.

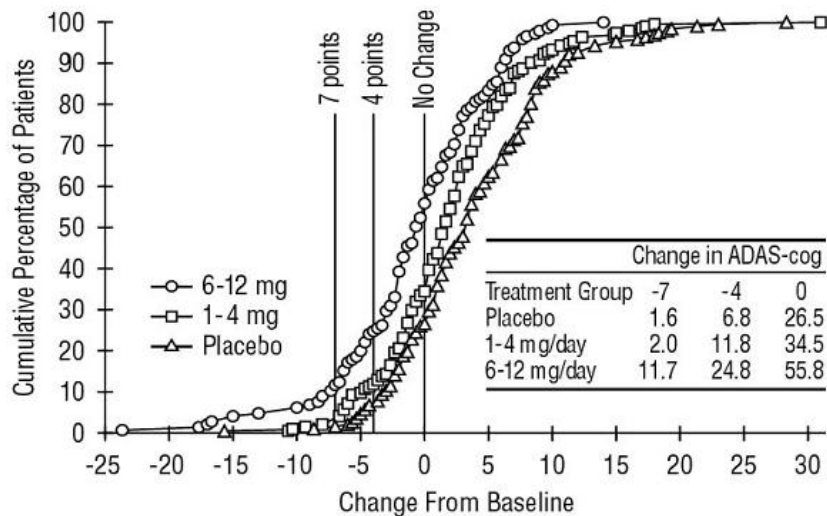
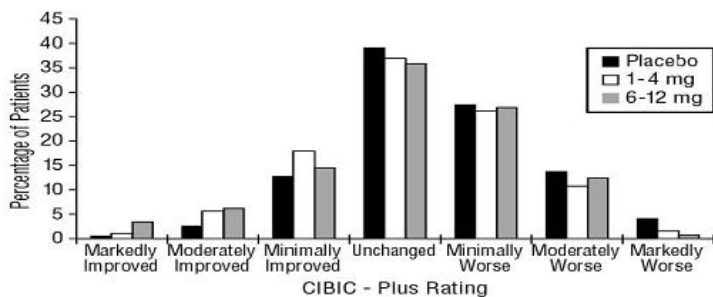


Figure 3 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the 3 treatment groups who completed 26 weeks of treatment. The mean rivastigmine tartrate-placebo differences for these groups of patients in the mean rating of change from baseline were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

Figure 3 Frequency Distribution of CIBIC-Plus Scores at Week 26 in Study 1



Global 26-Week Study in Mild to Moderate Alzheimer's Disease (Study 2)

In a second study of 26 weeks duration, 725 patients were randomized to either a dose range of 1 to 4 mg or 6 mg to 12 mg of rivastigmine tartrate 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.

Figure 4 illustrates the time course for the change from baseline in ADAS-cog scores for all 3 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-treated patients compared to the patients on placebo were 0.2 and 2.6 units for the 1 mg to 4 mg and 6 mg to 12 mg treatments, respectively. The 6 mg to 12 mg per day group was statistically significantly superior to placebo, as well as to the 1 to 4 mg/day group. The difference between the 1 mg to 4 mg per 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

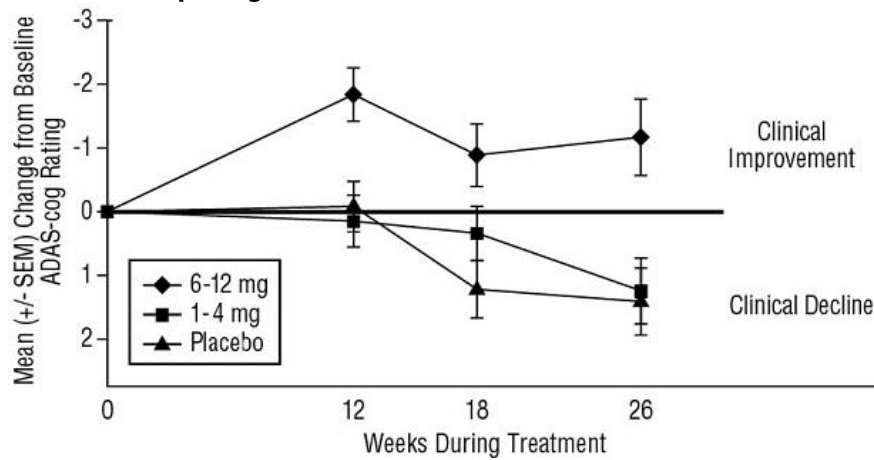


Figure 5 illustrates the cumulative percentages of patients from each of the 3 treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Similar to the U.S. 26-week study, the curves demonstrate that both patients assigned to rivastigmine tartrate and placebo have a wide range of responses, but that the 6 mg to 12 mg per day rivastigmine tartrate 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 mg-4 mg 86%, and 6 mg-12 mg 67%.

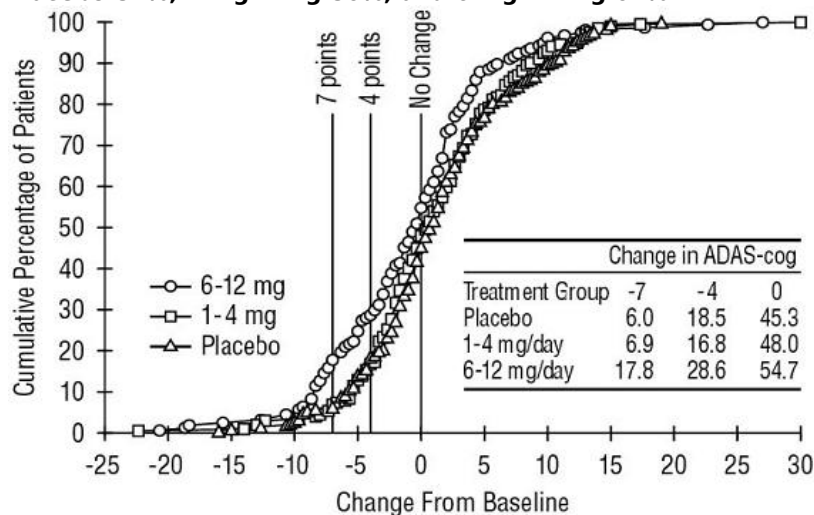
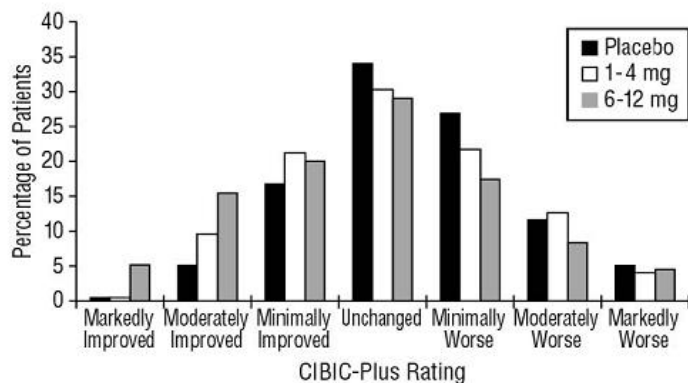


Figure 6 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the 3 treatment groups who completed 26 weeks of treatment. The mean rivastigmine tartrate-placebo differences for these groups of patients for the mean rating of change from baseline were 0.14 units and 0.41 units for 1 mg to 4 mg and 6 mg to 12 mg of rivastigmine tartrate, respectively. The mean ratings for the 6 mg to 12 mg per day group were statistically significantly superior to placebo. The comparison of the mean ratings for the 1 mg to 4 mg per day group and placebo group was not statistically significant.

Figure 6 Frequency Distribution of CIBIC-Plus Scores at Week 26 in Study 2



U.S. Fixed-Dose Study in Mild to Moderate Alzheimer’s Disease (Study 3)

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

Mild to Moderate Parkinson’s Disease Dementia

International 24-Week Study (Study 4)

The effectiveness of rivastigmine tartrate as a treatment for dementia associated with Parkinson’s disease is demonstrated by the results of 1 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 years. 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%.

This study used a dual outcome assessment strategy to evaluate the effectiveness of rivastigmine tartrate.

The ability of rivastigmine tartrate to improve cognitive performance was assessed with the ADAS-cog.

The ability of rivastigmine tartrate 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 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”.

In this study, 541 patients were randomized to a dose range of 3 mg to 12 mg of rivastigmine tartrate 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.

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-treated patients compared to the patients on placebo was 3.8 points. This treatment difference was statistically significant in favor of rivastigmine tartrate when compared to placebo.

Figure 7 Time Course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment in Study 4

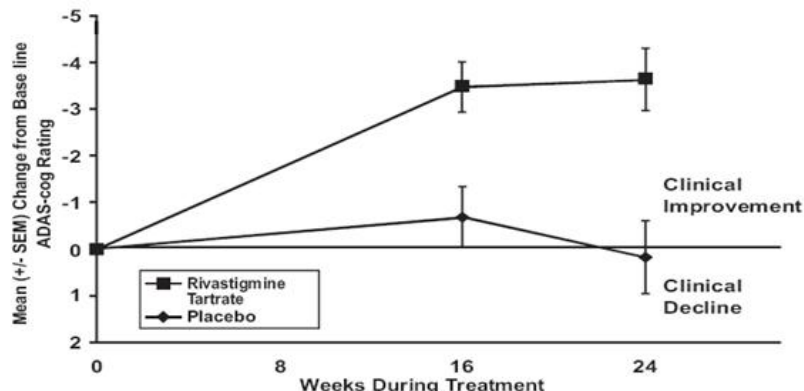
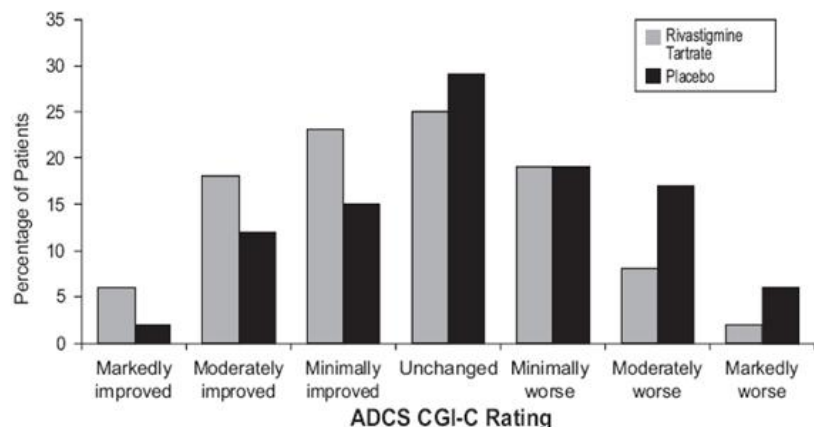


Figure 8 is a histogram of the distribution of patients' scores on the ADCS-CGIC (Alzheimer's Disease Cooperative Study - Clinician's Global Impression of Change) at 24 weeks. The mean difference in change scores between the rivastigmine tartrate and placebo groups from baseline was 0.5 points. This difference was statistically significant in favor of rivastigmine tartrate treatment.

Figure 8 Distribution of ADCS-CGIC Scores for Patients Completing 24 Weeks of Treatment in Study 4



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

16 HOW SUPPLIED/STORAGE AND HANDLING

Rivastigmine Tartrate Capsules USP

Rivastigmine Tartrate Capsules equivalent to 1.5 mg, 3 mg, 4.5 mg, or 6 mg of rivastigmine base are available as follows:

1.5 mg Capsule - Pale yellow opaque / pale yellow opaque, size '2' hard gelatin capsules radially imprinted with 'A' on cap and '116' on body with black ink, filled with white to off - white free flowing powder.

NDC 46708-063-30 Bottle of 30 Capsules

NDC 46708-063-60 Bottle of 60 Capsules

NDC 46708-063-71 Bottle of 500 Capsules

NDC 46708-063-91 Bottle of 1000 Capsules

NDC 46708-063-10 Unit Dose Capsules of 100 (Blisters of 10)

3 mg Capsule - Orange opaque / Orange opaque, size '2' hard gelatin capsules radially imprinted with 'A' on cap and '117' on body with black ink, filled with white to off - white

free flowing powder.

NDC 46708-064-30 Bottle of 30 Capsules
NDC 46708-064-60 Bottle of 60 Capsules
NDC 46708-064-71 Bottle of 500 Capsules
NDC 46708-064-91 Bottle of 1000 Capsules
NDC 46708-064-10 Unit Dose Capsules of 100 (Blisters of 10)

4.5 mg Capsule - Coral red opaque / coral red opaque, size '2' hard gelatin capsules radially imprinted with 'A' on cap and '118' on body with black ink, filled with white to off - white free flowing powder.

NDC 46708-065-30 Bottle of 30 Capsules
NDC 46708-065-60 Bottle of 60 Capsules
NDC 46708-065-71 Bottle of 500 Capsules
NDC 46708-065-91 Bottle of 1000 Capsules
NDC 46708-065-10 Unit Dose Capsules of 100 (Blisters of 10)

6 mg Capsule - Orange opaque / coral red opaque, size '2' hard gelatin capsules radially imprinted with 'A' on cap and '119' on body with black ink, filled with white to off - white free flowing powder.

NDC 46708-066-30 Bottle of 30 Capsules
NDC 46708-066-60 Bottle of 60 Capsules
NDC 46708-066-71 Bottle of 500 Capsules
NDC 46708-066-91 Bottle of 1000 Capsules
NDC 46708-066-10 Unit Dose Capsules of 100 (Blisters of 10)

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Store in a tight container.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Instructions for Use)

Gastrointestinal Adverse Reactions

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 [see *Warnings and Precautions (5.1)*].

Skin Reactions

Caregivers and patients should be advised that allergic skin reactions have been reported in association with rivastigmine tartrate regardless of formulation (capsules, oral solution or transdermal patch). In case of skin reaction while taking Rivastigmine tartrate capsules, patients should consult with their physician immediately [see *Warnings and Precautions (5.2)*].

Concomitant Use of Drugs with Cholinergic Action

Caregivers and patients should be advised that cholinomimetics, including rivastigmine, may exacerbate or induce extrapyramidal symptoms. Worsening in patients with Parkinson's disease, including an increased incidence or intensity of tremor, has been observed [see *Warnings and Precautions (5.3)*].

Manufactured by:

Alembic Pharmaceuticals Limited (Formulation Division),
Village Panelav, P. O. Tajpura, Near Baska,
Taluka-Halol, Panchmahal, Gujarat, India.

Revised: 01/2014

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL-1.5 mg

Rivastigmine Tartrate Capsules USP 1.5 mg (30 Capsules in 1 Bottle)
Each hard gelatin capsule contains rivastigmine tartrate USP, equivalent to 1.5 mg of rivastigmine base.
46708-063-30

*Each hard gelatin capsule contains rivastigmine tartrate USP, equivalent to 1.5 mg of rivastigmine base
See package insert for dosage information.
Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]
Dispense in a tight container (USP)
Keep this and all drugs out of the reach of children.

Manufactured by:
Alembic Pharmaceuticals Limited
(Formulation Division),
Village Panelav, P. O. Tajpura,
Near Baska, Taluka-Halol,
Panchmahal, Gujarat, India.

NDC 46708-063-30
**Rivastigmine
Tartrate
Capsules, USP**
1.5 mg *
Rx only 30 Capsules

Alembic

NDC 46708-063-30
Mfg. Lic. No. G/959
Batch:
Expiry:
2006115
01/2015

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL-3 mg

Rivastigmine Tartrate Capsules USP 3 mg (30 Capsules in 1 Bottle)
Each hard gelatin capsule contains rivastigmine tartrate USP, equivalent to 3 mg of rivastigmine base.
46708-064-30

*Each hard gelatin capsule contains rivastigmine tartrate USP, equivalent to 3 mg of rivastigmine base
See package insert for dosage information.
Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]
Dispense in a tight container (USP)
Keep this and all drugs out of the reach of children.

Manufactured by:
Alembic Pharmaceuticals Limited
(Formulation Division),
Village Panelav, P. O. Tajpura,
Near Baska, Taluka-Halol,
Panchmahal, Gujarat, India.

NDC 46708-064-30
**Rivastigmine
Tartrate
Capsules, USP**
3 mg *
Rx only 30 Capsules

Alembic

NDC 46708-064-30
Mfg. Lic. No. G/959
Batch:
Expiry:
2006117
01/2015

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL-4.5 mg

Rivastigmine Tartrate Capsules USP 4.5 mg (30 Capsules in 1 Bottle)
Each hard gelatin capsule contains rivastigmine tartrate USP, equivalent to 4.5 mg of rivastigmine base.
46708-065-30

*Each hard gelatin capsule contains rivastigmine tartrate USP, equivalent to 4.5 mg of rivastigmine base

See package insert for dosage information.

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]

Dispense in a tight container (USP)

Keep this and all drugs out of the reach of children.

Manufactured by:
Alembic Pharmaceuticals Limited
(Formulation Division),
Village Panelav, P. O. Tajpura,
Near Baska, Taluka-Halol,
Panchmahal, Gujarat, India.

NDC 46708-065-30

Rivastigmine Tartrate Capsules, USP

4.5 mg *

Rx only 30 Capsules

Alembic

46708-065-30

Mfg. Lic. No. G/959

Batch: 35596

Expiry: 01/2015

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL-6 mg

Rivastigmine Tartrate Capsules USP 6 mg (30 Capsules in 1 Bottle)
Each hard gelatin capsule contains rivastigmine tartrate USP, equivalent to 6 mg of rivastigmine base.

46708-066-30

*Each hard gelatin capsule contains rivastigmine tartrate USP, equivalent to 6 mg of rivastigmine base

See package insert for dosage information.

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]

Dispense in a tight container (USP)

Keep this and all drugs out of the reach of children.

Manufactured by:
Alembic Pharmaceuticals Limited
(Formulation Division),
Village Panelav, P. O. Tajpura,
Near Baska, Taluka-Halol,
Panchmahal, Gujarat, India.

NDC 46708-066-30

Rivastigmine Tartrate Capsules, USP

6 mg *

Rx only 30 Capsules

Alembic

46708-066-30

Mfg. Lic. No. G/959

Batch: 20006121

Expiry: 01/2015

RIVASTIGMINE TARTRATE

rivastigmine tartrate capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:46708-063
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RIVASTIGMINE TARTRATE (UNII: 9IY2357JPE) (RIVASTIGMINE - UNII:PKI06M3IW0)	RIVASTIGMINE	1.5 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6130)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

Product Characteristics

Color	YELLOW (pale yellow opaque)	Score	no score
Shape	CAPSULE	Size	18mm
Flavor		Imprint Code	B;793
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-063-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
2	NDC:46708-063-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
3	NDC:46708-063-71	500 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
4	NDC:46708-063-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
5	NDC:46708-063-10	100 in 1 BOX, UNIT-DOSE	06/13/2012	
5	NDC:46708-063-11	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091689	06/13/2012	

RIVASTIGMINE TARTRATE

rivastigmine tartrate capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:46708-064
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
RIVASTIGMINE TARTRATE (UNII: 9IY2357JPE) (RIVASTIGMINE - UNII:PKI06M3IW0)	RIVASTIGMINE	3 mg

Inactive Ingredients	
Ingredient Name	Strength
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
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	B;794
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-064-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
2	NDC:46708-064-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
3	NDC:46708-064-71	500 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
4	NDC:46708-064-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
5	NDC:46708-064-10	100 in 1 BOX, UNIT-DOSE	06/13/2012	
5	NDC:46708-064-11	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091689	06/13/2012	

RIVASTIGMINE TARTRATE

rivastigmine tartrate capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:46708-065
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RIVASTIGMINE TARTRATE (UNII: 9IY2357JPE) (RIVASTIGMINE - UNII:PKI06M3IW0)	RIVASTIGMINE	4.5 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics

Color	RED (Coral red opaque)	Score	no score
Shape	CAPSULE	Size	18mm
Flavor		Imprint Code	B;795
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-065-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
2	NDC:46708-065-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
3	NDC:46708-065-71	500 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
4	NDC:46708-065-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
5	NDC:46708-065-10	100 in 1 BOX, UNIT-DOSE	06/13/2012	
5	NDC:46708-065-11	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091689	06/13/2012	

RIVASTIGMINE TARTRATE

rivastigmine tartrate capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:46708-066
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name		Basis of Strength	Strength	
RIVASTIGMINE TARTRATE (UNII: 9IY2357JPE) (RIVASTIGMINE - UNII:PKI06M3IW0)		RIVASTIGMINE	6 mg	
Inactive Ingredients				
Ingredient Name		Strength		
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3W0)				
MAGNESIUM STEARATE (UNII: 70097M6I30)				
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)				
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)				
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)				
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)				
FERRIC OXIDE RED (UNII: 1K09F3G675)				
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)				
Product Characteristics				
Color	ORANGE (Orange opaque) , RED (Coral red opaque)	Score	no score	
Shape	CAPSULE	Size	18mm	
Flavor		Imprint Code	B;796	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-066-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
2	NDC:46708-066-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
3	NDC:46708-066-71	500 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
4	NDC:46708-066-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	06/13/2012	
5	NDC:46708-066-10	100 in 1 BOX, UNIT-DOSE	06/13/2012	
5	NDC:46708-066-11	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA091689	06/13/2012		

Labeler - Alembic Pharmaceuticals Limited (650574663)

Establishment

Name	Address	ID/FEI	Business Operations
Alembic Pharmaceuticals Limited		650574671	MANUFACTURE(46708-063, 46708-064, 46708-065, 46708-066)

Revised: 1/2023

Alembic Pharmaceuticals Limited