CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-823/S-003
21-025/S-003

APPROVAL LETTER

NDA 20-823/S-003
NDA 21-025/S-003

Novartis Pharmaceuticals Corporation
Attention: James Rawls, Pharm.D
59 Route 10
East Hanover, NJ 07936

JAN 05 2001

Dear Dr. Rawls:

Please refer to your supplemental new drug applications dated November 3, 2000, received November 6, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exelon (rivastigmine tartrate) Capsules and Oral Solution.

We also acknowledge receipt of your submissions dated November 29; and December 11 & 22, 2000, submitted to each of these supplemental new drug applications.

These "Changes Being Effected" supplemental new drug applications were prompted by a post-marketing report of esophageal rupture after severe vomiting and provide for revision of the WARNINGS, PRECAUTIONS and DOSAGE and ADMINISTRATION sections of the package insert to provide guidelines for reinitiating therapy in patients who have interrupted treatment with Exelon to reduce the risk of severe vomiting. Additionally, the ADVERSE REACTIONS section has been revised to include a report of a case of Stevens-Johnson syndrome.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter. Please note that the enclosed labeling text utilizes a strikeout/redline format to indicate where the changes to the previously approved label have been made. Finally, we have attached labeling text for the capsule application only and ask that similar revisions be made to the oral solution labeling.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according

to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-823/S-003, 21-025/S-003." Approval of these submissions by FDA is not required before the labeling is used.

We note that you intend to send a letter communicating important information about these drug products (i.e., a "Dear Health Care Practitioner" letter) to physicians and others responsible for patient care under the provisions of 21 CFR 200.5(c)(1) "IMPORTANT DRUG WARNING". We request that you submit a copy of the final letter and mailing envelope to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Mr. Robbin Nighswander, R.Ph., Senior Regulatory Management Officer, at (301) 594-5531.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-823/S-003
21-025/S-003

FINAL PRINTED LABELING

NOVARTIS

T2000-11
89007401

Exelon®

(rivastigmine tartrate)

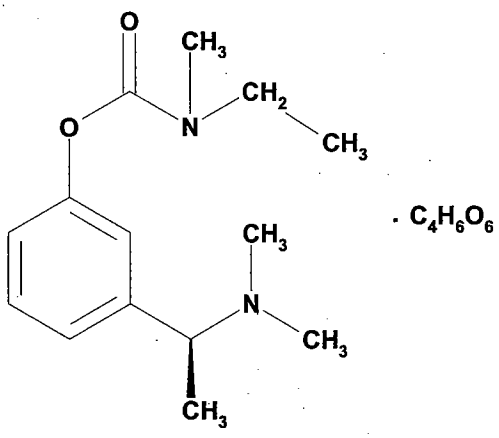
Capsules

Rx Only

Prescribing Information

DESCRIPTION

Exelon® (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.



Exelon is supplied as capsules containing rivastigmine tartrate, equivalent to 1.5, 3.0, 4.5 and 6.0 mg of rivastigmine base for oral administration. Inactive ingredients are hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and silicone dioxide. Each hard-gelatin capsule contains gelatin, titanium dioxide and red and/or yellow iron oxides.

CLINICAL PHARMACOLOGY

Mechanism of Action

Pathological changes in Dementia of the Alzheimer type 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, Exelon's 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% five hours after dosing.

Clinical Trial Data

The effectiveness of Exelon® (rivastigmine tartrate) as a treatment for Alzheimer's Disease is demonstrated by the results of two 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 Exelon trials was 73 years with a range of 41-95. 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 Exelon was evaluated using a dual outcome assessment strategy.

The ability of Exelon 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 suggest that they gain 6-12 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 Exelon trials was approximately 3-8 units per year.

The ability of Exelon to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-Plus. The CIBIC-Plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-Plus reflect clinical experience from the trial or trials in which it was used and can not be compared directly with the results of CIBIC-Plus evaluations from other clinical trials. The CIBIC-Plus used in the Exelon 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 seven point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening." The CIBIC-Plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

U.S. Twenty-Six-Week Study

In a study of 26 weeks duration, 699 patients were randomized to either a dose range of 1-4 mg or 6-12 mg of Exelon 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 Exelon-treated patients compared to the patients on placebo were 1.9 and 4.9 units for the 1-4 mg and 6-12 mg treatments, respectively. Both treatments were statistically significantly superior to placebo and the 6-12 mg/day range was significantly superior to the 1-4 mg/day range.

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

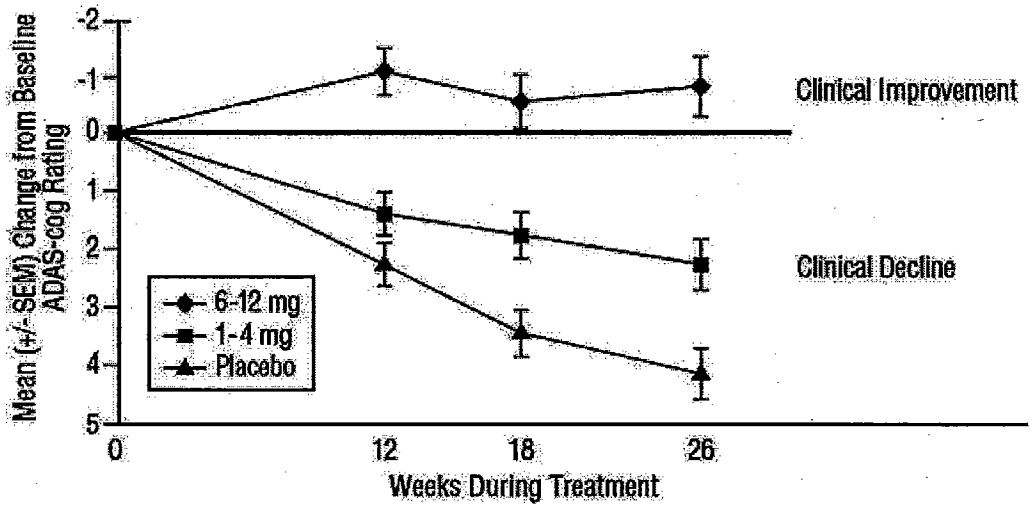
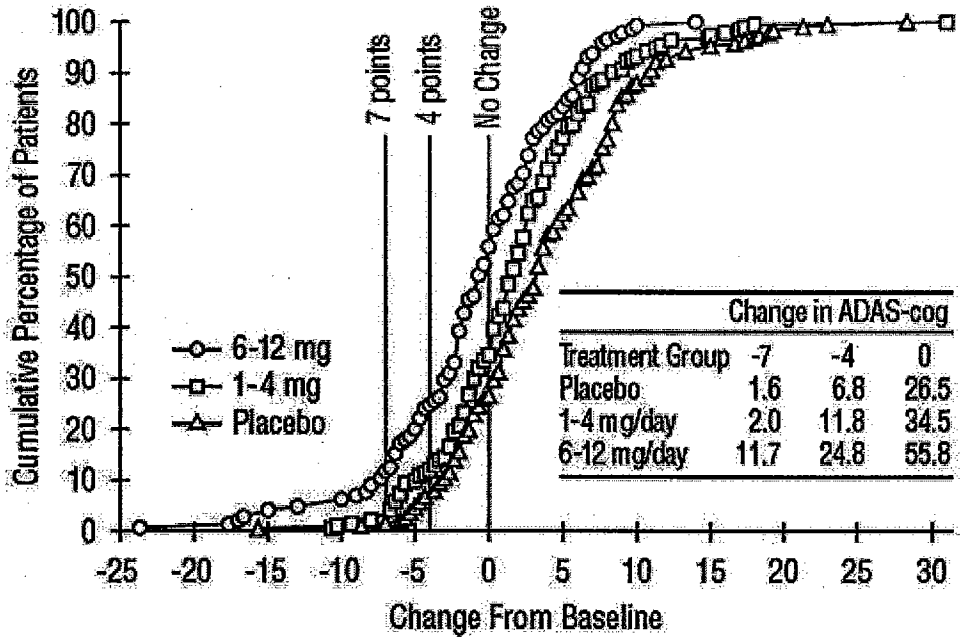


Figure 2 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified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

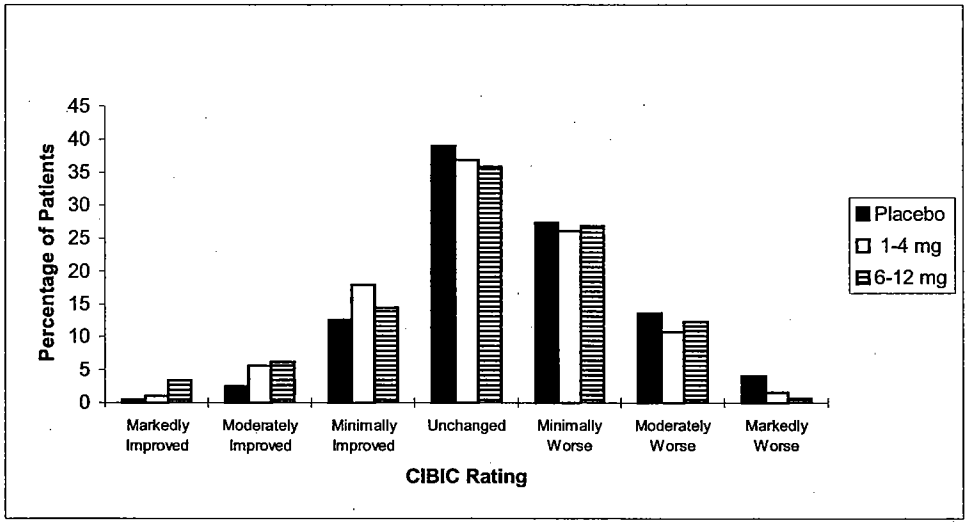
The curves demonstrate that both patients assigned to Exelon and placebo have a wide range of responses, but that the Exelon groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious 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%, 1-4 mg 85%, and 6-12 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 Exelon-placebo differences for these groups of patients in the mean rating of change from baseline were 0.32 units and 0.35 units for 1-4 mg and 6-12 mg of Exelon, respectively. The mean ratings for the 6-12 mg/day and 1-4 mg/day groups were statistically significantly superior to placebo. The differences between the 6-12 mg/day and the 1-4 mg/day groups were statistically significant.

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



Global Twenty-Six-Week Study

In a second study of 26 weeks duration, 725 patients were randomized to either a dose range of 1-4 mg or 6-12 mg of Exelon 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 Exelon-treated patients compared to the patients on placebo were 0.2 and 2.6 units for the 1-4 mg and 6-12 mg treatments, respectively. The 6-12 mg/day group was statistically significantly superior to placebo, as well as to the 1-4 mg/day group. The difference between the 1-4 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

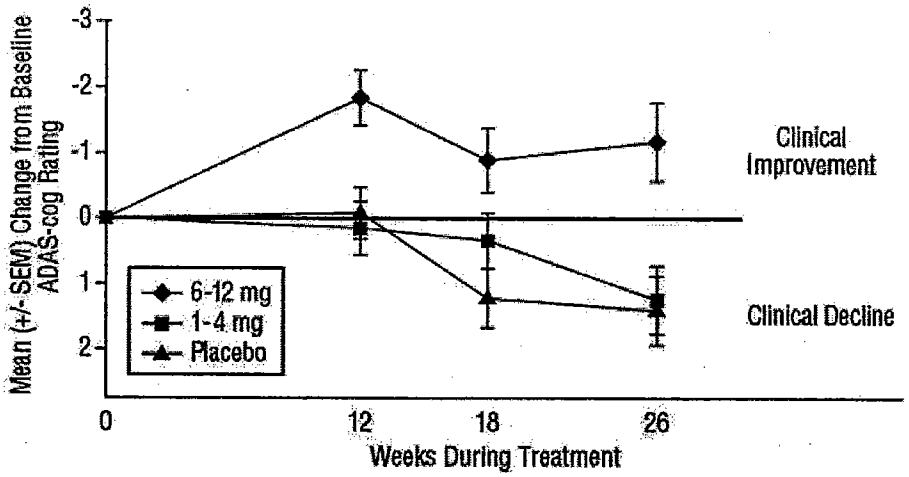
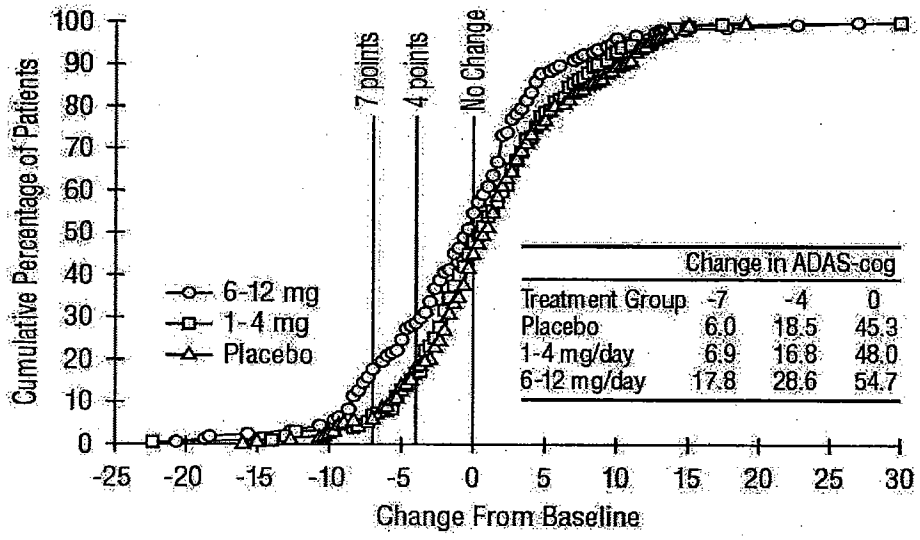


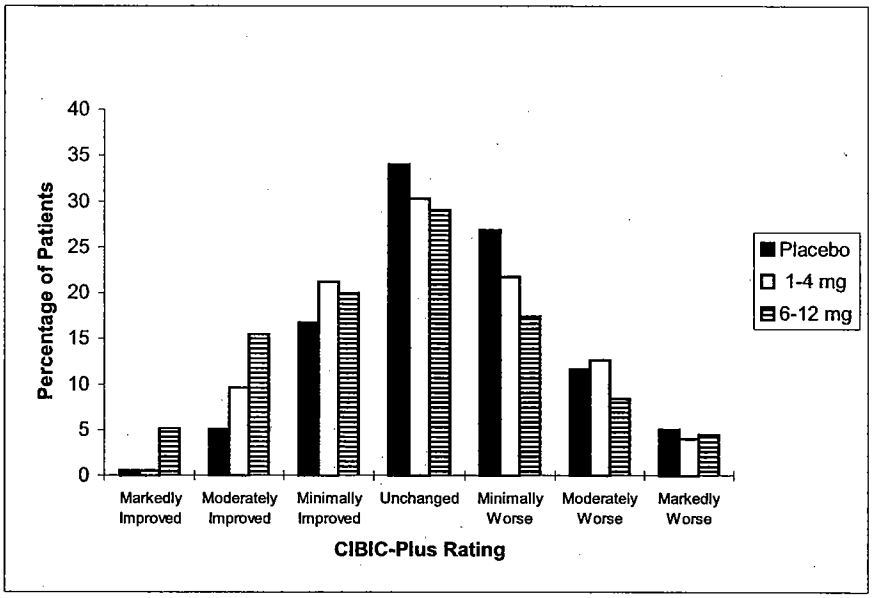
Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Similar to the U.S. 26-week study, the curves demonstrate that both patients assigned to Exelon and placebo have a wide range of responses, but that the 6-12 mg/day Exelon 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%, 1-4 mg 86%, and 6-12 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 Exelon-placebo differences for these groups of patients for the mean rating of change from baseline were 0.14 units and 0.41 units for 1-4 mg and 6-12 mg of Exelon, respectively. The mean ratings for the 6-12 mg/day group was statistically significantly superior to placebo. The comparison of the mean ratings for the 1-4 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 Exelon 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 Exelon dose groups and placebo for the analysis of the CIBIC-Plus mean rating of change. Although no significant differences were observed between Exelon treatment groups, there was a trend toward numerical superiority with higher doses.

Age, Gender and Race: Patient's age, gender, or race did not predict clinical outcome to Exelon 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 Exelon with food delays absorption (t_{max}) by 90 min, 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 1.8-2.7 L/kg. Rivastigmine penetrates the blood brain barrier, reaching CSF peak concentrations in 1.4-2.6 hours. Mean $AUC_{1\text{-}12hr}$ ratio of CSF/plasma averaged 40 ± 0.5% following 1-6 mg BID doses.

Rivastigmine is about 40% bound to plasma proteins at concentrations of 1-400 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 1-400 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 5-6) and moderate (n=3, Child-Pugh score 7-9) 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=10-50 mL/min) than in healthy subjects (n=10, GFR≥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≥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 Exelon, 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 Exelon.

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 Exelon 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 Exelon.

Effect of Other Drugs on the Metabolism of Exelon: 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), non-steroidal 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 Exelon and these agents.

INDICATIONS AND USAGE

Exelon® (rivastigmine tartrate) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS

Exelon® (rivastigmine tartrate) is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation (see DESCRIPTION).

WARNINGS

Gastrointestinal Adverse Reactions

Exelon® (rivastigmine tartrate) 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 post-marketing 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 an Exelon dose in the therapeutic range of 6-12 mg/day (n=1189) developed nausea (compared with 12% in placebo). A total of 31% of Exelon-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 Exelon-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 Exelon (greater than 9 mg/day) had weight loss of 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 an Exelon dose of 6-12 mg/day, 17% developed anorexia compared to 3% of the placebo patients. Neither the time course or 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 Exelon have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Anesthesia

Exelon 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, Exelon 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 6–12 mg/day of Exelon, compared to 2% of placebo patients.

Genitourinary

Although this was not observed in clinical trials of Exelon, 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, Exelon 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.

Drug-Drug Interactions

Effect of Exelon® (rivastigmine tartrate) 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 Exelon.

Effect of Other Drugs on the Metabolism of Exelon: 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 per day on a mg/m^2 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/per day on a mg/m^2 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/m^2 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/m^2 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/m^2 basis. There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Exelon 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. Exelon has no indication for use in nursing mothers.

Pediatric Use

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

ADVERSE REACTIONS

Adverse Events Leading to Discontinuation

The rate of discontinuation due to adverse events in controlled clinical trials of Exelon® (rivastigmine tartrate) was 15% for patients receiving 6-12 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 Exelon 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 6-12 mg/day Exelon® Using a Forced Dose Titration

Study Phase	Titration		Maintenance		Overall	
	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1189)	Placebo (n=788)	Exelon ≥6-12 mg/day (n=987)	Placebo (n=868)	Exelon ≥6-12 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 Exelon

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 Exelon's cholinergic effects. These include nausea, vomiting, anorexia, dyspepsia, and asthenia.

Gastrointestinal Adverse Reactions

Exelon 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 Exelon doses of 6-12 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 on 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 Exelon® (6-12 mg/day) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=868)	Exelon® (6-12 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 Exelon 6-12 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 infections, infection (general), coughing, pharyngitis, bronchitis, rash (general), urinary incontinence.

Other Adverse Events Observed During Clinical Trials

Exelon 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 10-12 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 Exelon. 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 Exelon 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, paraesthesia, convulsions. *Infrequent:* Paresis, apraxia, aphasia, dysphonia, hyperkinesia, hyperreflexia, hypertonia, hypoesthesia, hypokinesia, migraine, neuralgia, nystagmus, peripheral neuropathy.

Endocrine System: *Infrequent:* Goitre, 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, hyperlipernia, 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, dermatitis contact.

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, thrombophlebitis deep, aneurysm, hemorrhage intracranial.

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

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

Post-Introduction Reports

Voluntary reports of adverse events temporally associated with Exelon 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 Exelon® (rivastigmine tartrate) has a short plasma half-life of about one hour and a moderate duration of acetylcholinesterase inhibition of 8-10 hours, it is recommended that in cases of asymptomatic overdoses, no further dose of Exelon 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 Exelon, 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 Exelon, 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

The dosage of Exelon® (rivastigmine tartrate) shown to be effective in controlled clinical trials is 6-12 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 Exelon is 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of two 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).

Exelon should be taken with meals in divided doses in the morning and evening.

HOW SUPPLIED

Exelon® (rivastigmine tartrate) capsules equivalent to 1.5 mg, 3.0 mg, 4.5 mg, or 6.0 mg of rivastigmine base are available as follows:

1.5 mg Capsule – yellow, "Exelon 1,5 mg" is printed in red on the body of the capsule.

Bottles of 60 ..... NDC 0078-0323-44
Bottles of 500 ..... NDC 0078-0323-08
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0078-0323-06

3.0 mg Capsule – orange, "Exelon 3 mg" is printed in red on the body of the capsule.

Bottles of 60 ..... NDC 0078-0324-44
Bottles of 500 ..... NDC 0078-0324-08
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0078-0324-06

4.5 mg Capsule – red, "Exelon 4,5 mg" is printed in white on the body of the capsule.

Bottles of 60 ..... NDC 0078-0325-44
Bottles of 500 ..... NDC 0078-0325-08
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0078-0325-06

6.0 mg Capsule - orange and red, "Exelon 6 mg" is printed in red on the body of the capsule.

Bottles of 60 ..... NDC 0078-0326-44
Bottles of 500 ..... NDC 0078-0326-08
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0078-0326-06

Store below 77°F (25°C) in a tight container.

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NOVARTIS

Manufactured by
Novartis Pharma AG
Basle, Switzerland

Manufactured for
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-823/S-003
21-025/S-003

MEDICAL REVIEW

Review and Evaluation of Clinical Data

NDA (Serial Number)	**20823/ 21025**
Sponsor:	**Novartis**
Drug:	**Exelon**
Indication:	**Alzheimer's Disease**
Material Submitted:	**Labeling Change**
Correspondence Date:	**11/3/00**
Date Received / Agency:	**11/6/00**
Date Review Completed	**12/21/00**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This submission contains changes to the package insert to Exelon® proposed by the sponsor in response to recent letters from this Division.

Exelon® (rivastigmine) is a drug approved by this Agency on 4/21/00 for the treatment of mild to moderate Alzheimer's Disease. Please refer to the primary reviews of NDAs #s 20823 (for the capsule formulation) and 21025 (for the oral solution formulation) for full details.

The relevant letters from this Division to the sponsor are as follows:

- A letter dated 10/13/00 recommending changes to the label; this letter was based on a post-marketing adverse event report of vomiting with esophageal rupture in a patient in whom treatment with Exelon® was restarted at a higher-than-minimum-recommended after complete treatment interruption for 8 weeks. Prior to treatment interruption the patient had been titrated to an Exelon® dose of 9 mg/day.
- A letter dated 10/27/00 recommending a change to the label based on a post-marketing adverse event report of Stevens-Johnson syndrome occurring in association with Exelon® use.

For further details of these adverse event reports see my reviews completed 10/10/00 and 10/11/00, on which the Division's letters dated 10/13/00 and 10/27/00, respectively, are based.

This submission is the first proposed change to labeling since Exelon® was originally approved for marketing in this country

2. Contents Of Current Submission

The current submission contains

- Highlighted labeling revisions proposed by the sponsor
- Final printed labeling
- A "Dear Doctor" letter
- Supportive data

3. Contents Of Agency Letter Dated 10/13/00

Based on the single case report of esophageal rupture linked to re-initiation of Exelon® at a higher-than-recommended dose the Division had recommended the following changes to labeling

3.1 WARNINGS Section:

The following text should replace the existing text of this section up to the Nausea and Vomiting paragraph and should remain bolded.

Gastrointestinal Adverse Reactions:

EXELON® use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. ———————

Nausea and Vomiting: .....

3.2 PRECAUTIONS: Information For Patients And Caregivers Subsection:

This section should be revised as follows:

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 ——————— next dose should not be administered until they have discussed this with the physician.

3.3 DOSAGE And ADMINISTRATION Section:

Revise the 2nd paragraph of this section as follows:

——————— If this dose is well tolerated, after a minimum of two 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, ——— ——————— The maximum dose is 6 mg BID (12 mg/day).

4. Contents Of Agency Letter Dated 10/27/00

Based on the single case report of Stevens-Johnson syndrome linked to use of Exelon® the Division had recommended the following change to the labeling

4.1 ADVERSE REACTIONS Section

The following subsection should be added to the labeling at the end of this section
Post-Introduction Reports
Voluntary reports of adverse events temporally associated with Exelon® that have been received since market introduction that are not listed above, [redacted]

Stevens-Johnson syndrome.

5. Labeling Changes Proposed By Sponsor In Current Submission

Deletions made by the sponsor are shown using the strikethrough feature.
Additions made by the sponsor are highlighted in red

5.1 WARNINGS Section:

Gastrointestinal Adverse Reactions:

EXELON® use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. [redacted]

Nausea and Vomiting: .....

5.2 PRECAUTIONS: Information For Patients And Caregivers Subsection:

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 [redacted] therapy has been interrupted for more than [redacted] the next dose should not be administered until they have discussed this with the physician.

5.3 ADVERSE REACTIONS Section

Post-Introduction Reports

Voluntary reports of adverse events temporally associated with Exelon® that have been received since market introduction that are not listed above, [redacted]

Skin and Appendages: Stevens-Johnson syndrome

5.4 DOSAGE And ADMINISTRATION Section:

[redacted] The starting dose of EXELON® is [redacted] 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of two 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 [redacted] The maximum dose is 6 mg BID (12 mg/day).

EXELON® should be taken with meals [redacted] in divided doses in the morning and evening

Reviewer's Note: The changes that have been made by the sponsor to the last sentence above in the "Dosage and Administration" section reflect alterations to the original labeling and not to any changes proposed by this Division in the letters dated 10/13/00 and 10/27/00.

6. Basis For Sponsor's Proposed Labeling Change

The supportive data cited in this section are only in reference to the report of vomiting with esophageal rupture

6.1 Introduction

In response to the Division's letter of 10/13/00 the sponsor has done the following

- Estimated the extent of exposure to Exelon®
- Attempted to determine the frequency of esophageal rupture
- Used an analysis of data from Phase III clinical trials of Exelon® to make recommendations about resuming treatment after interruption of dosing.

6.2 Extent Of Exposure To Exelon®

Based on sales of units of Exelon® (capsule and solution formulations) worldwide the sponsor estimates that about [redacted] patients have been exposed to Exelon®

6.3 Frequency Of Esophageal Rupture In Patients Taking Exelon®

The sponsor has conducted a search for the events esophageal rupture and vomiting within the Novartis Clinical Safety and Epidemiology spontaneous reports and serious adverse events databases. All cases of vomiting were reviewed. **No additional cases of esophageal rupture were noted.**

6.4 Dose Interruptions In Phase III Trials

6.4.1 Approach To Dose Interruptions In Phase III Trials

In Phase III trials of Exelon®, there were protocol-specified recommendations for resuming treatment after dose interruptions. These recommendations were consistent across the open-label studies B 355, B 356, B 353 and B 305, but not across the randomized, double-blind, placebo-controlled studies B 303, B 304, B 351 and B 352

An example of such recommendations has been provided; this example is drawn from the protocol for the B 355 study. I have summarized these recommendations in the table below.

DOSES MISSED	CURRENT DOSE	ACTION
≤ 6	≤ 3 mg b.i.d	Continue Or Restart at the next lower dose
≤ 6	> 3 mg b.i.d	
≥ 6	≤ 3 mg b.i.d	
≥ 6	> 3 mg b.i.d	Retitrate starting at ≤ 3 mg b.i.d

6.4.2 Analysis Of Dose Interruptions

The analysis was

- Undertaken to determine the proportion of patients reporting adverse events (graded by severity and seriousness) when Exelon® was resumed after a dosing interruption
- Confined to adverse events starting within 7 days of resumption of treatment
- Based on 3 lengths of dosing interruption: > 3 days; > 7 days; and > 14 days

6.4.3 Results

The table below shows the number of patients and total interruptions in Phase III clinical studies categorized by duration of interruption and restarting dose

Number of Patients and Total Interruptions in Phase 3 Studies

	> 3 days		> 7 days		> 14 days	
Restarting Dose	Total Patients	Total Interruptions	Total Patients	Total Interruptions	Total Patients	Total Interruptions
	N	N	N	N	N	N
= 3 mg/day	51	53	31	32	16	17
> 3 mg/day	533	682	292	340	156	175
≥ 6 mg/day	444	555	240	276	133	150
≥ 9 mg/day	185	223	97	113	61	68

The next tables show the proportion of patients reporting selected adverse events within 7 days of restarting Exelon® following dose interruptions of > 3 days, > 7 days and > 14 days

Proportion of Patients in Phase 3 Studies Reporting Selected Adverse Events within Seven Days of Restarting Exelon Following a Dose Interruption of >3 Days by Restarting Dose

	= 3 mg/day N = 51 n (%)	> 3 mg/day N = 533 n (%)	≥ 6 mg/day N = 444 n (%)	≥ 9 mg/day N = 185 n (%)
Any Adverse Event (AE)	10 (20)	121 (23)	96 (22)	35 (19)
Any Severe AE	0 (0)	9 (2)	5 (1)	1 (1)
Nausea	3 (6)	28 (5)	22 (5)	7 (4)
Severe Nausea	0 (0)	1 (<1)	0 (0)	0 (0)
Vomiting	1 (2)	23 (4)	19 (4)	8 (4)
Severe Vomiting	0 (0)	2 (<1)	1 (<1)	0(0)
Any Serious AE	0 (0)	8 (2)	6 (1)	3 (2)

Proportion of Patients in Phase 3 Studies Reporting Selected Adverse Events within Seven Days of Restarting Exelon Following a Dose Interruption of >7 Days by Restarting Dose

	= 3 mg/day N = 31 n (%)	> 3 mg/day N = 292 n (%)	≥ 6 mg/day N = 240 n (%)	≥ 9 mg/day N = 97 n (%)
Any Adverse Event (AE)	5 (16)	51 (17)	40 (17)	16 (16)
Any Severe AE	0 (0)	4 (1)	2 (1)	1 (1)
Nausea	2 (6)	9 (3)	7 (3)	4 (4)
Severe Nausea	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	0 (0)	5 (2)	5 (2)	4 (4)
Severe Vomiting	0 (0)	0 (0)	0 (0)	0(0)
Any Serious AE	0 (0)	5 (2)	4 (2)	2 (2)

Proportion of Patients in Phase 3 Studies Reporting Selected Adverse Events within Seven Days of Restarting Exelon Following a Dose Interruption of >14 Days by Restarting Dose

	= 3 mg/day N = 16 n (%)	> 3 mg/day N = 156 n (%)	≥ 6 mg/day N = 133 n (%)	≥ 9 mg/day N = 61 n (%)
Any Adverse Event (AE)	3 (19)	24 (15)	21 (16)	9 (15)
Any Severe AE	0 (0)	3 (2)	2 (2)	1 (2)
Nausea	1 (6)	4 (3)	4 (3)	3 (5)
Severe Nausea	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	0 (0)	3 (2)	3 (2)	2 (3)
Severe Vomiting	0 (0)	0 (0)	0 (0)	0(0)
Any Serious AE	0 (0)	3 (2)	2 (2)	1 (2)

6.5 "Dear Doctor" Letter

The sponsor has proposed a "Dear Doctor" letter which is to have the heading

"

The key paragraphs in the letter are as follows:

There is limited experience related to restarting after an interruption of therapy at doses higher than the recommended starting dose. However to reduce the possibility of r

Patients should be titrated back to their maintenance dose as described in DOSAGE AND ADMINISTRATION section of the PI.

7. Comments

- Although I agree with the sponsor that esophageal rupture is a very rare adverse event in patients receiving Exelon®
  - **Such an adverse event is always life-threatening**
  - **In the specific case of vomiting with esophageal rupture reported it is virtually certain that Exelon® had a causal role**
- The sponsor's analysis of adverse events after dosing interruption does indicate that
  - Adverse events (including nausea, vomiting and all serious adverse events) that occur in the first week after dose resumption, are infrequent in those resuming Exelon® treatment after interruptions longer than 3 days.
  - Adverse events are infrequent regardless of the dose at which treatment is resumed or the duration of interruption of therapy under the conditions of the analysis.
- However
  - It is not clear how many patients on whom the analysis was performed had interruptions of treatment that were substantially longer than 14 days (e.g., 4-12 weeks). It might be expected that in patients in whom treatment was interrupted for a period as long as 8 weeks resumption of treatment at higher doses would be associated with a higher incidence of adverse events than in those in whom treatment was interrupted for merely 2 weeks
  - The frequency of adverse events fter resumption of Exelon® treatment in the population analyzed is also unclear
  - The sponsor's analysis does not provide a firm basis for the proposed recommendation that those whose Exelon® treatment has been interrupted for ould have their treatment resumed at the d. Nevertheless an interruption of treatment for greater thar does seem to be a reasonably prudent criterion for reinitiating treatment at the
- The sponsor's analysis does not provide any reassurance that the rare, but life-threatening and potentially preventable, adverse event of vomiting with esophageal rupture will not continue to occur, especially if treatment with Exelon® is resumed without titration after a significant dosing interruption
- The "Dear Doctor" letter does not state what new information has made it especially important to re-titrate dosing with the drug after treatment

interruptions of longer than [redacted], a reader of that letter will need to refer to the Post-Introduction Reports subsection of the Adverse Events section of the package insert to be aware that a patient taking Exelon® has had vomiting with esophageal rupture; the Post-Introduction Reports subsection of the prescribing information lacks prominence.

Given that the objective of the "Dear Doctor" letter and changes in label are to highlight both the need for re-titration of Exelon® after a significant interruption, and to explain the potential serious consequences of not doing so, I would argue that

- **The WARNINGS section of the label continues to be as recommended by the Division in our letter of 10/13/00**

[redacted]

- **The re-initiation of treatment with Exelon® [redacted] after an interruption in treatment of [redacted] should be specifically recommended in the DOSAGE AND ADMINISTRATION section of the label**
- **The "Dear Doctor" letter mentions that an [redacted]**

[redacted]

Appendix 1 contains labeling that I would recommend (only the sections of the label that have been altered beginning with the Division's letter of 10/13/00) are reproduced.

- The addition of Stevens-Johnson syndrome to the Post-Introduction Reports subsection of the Adverse Events section of the label is in accordance with the Division's recommendations and is acceptable.

Ranjit B. Mani, M.D.
Medical Reviewer

8. Appendix 1: Recommended Labeling

8.1 WARNINGS Section:

Gastrointestinal Adverse Reactions:

EXELON® use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. [redacted]

[redacted]

Nausea and Vomiting: .....

8.2 PRECAUTIONS: Information For Patients And Caregivers Subsection:

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 [redacted] the next dose should not be administered until they have discussed this with the physician.

8.3 ADVERSE REACTIONS Section

Post-Introduction Reports
Voluntary reports of adverse events temporally associated with Exelon® that have been received since market introduction that are not listed above, [redacted]

Skin and Appendages: Stevens-Johnson syndrome

8.4 DOSAGE And ADMINISTRATION Section:

The starting dose of EXELON® is 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of two 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 longe[redacted] titrated as described above (see WARNINGS). The maximum dose is 6 mg BID (12 mg/day).

EXELON® should be taken with meals in divided doses in the morning and evening

9. Addendum # 1; November 14, 2000

Yesterday the sponsor submitted changes to both the proposed labeling and the Dear Doctor letter in advance of a teleconference scheduled for today. The changes made are as follows:

9.1 WARNINGS Section

The following text (highlighted in blue) has been added to the first paragraph of this section

Gastrointestinal Adverse Reactions:

EXELON® 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 [redacted] with the lowest daily dose (see DOSAGE AND ADMINISTRATION)

9.2 Dear Doctor Letter

The following text (in blue) has been added to the second paragraph

[redacted] restarting Exelon® after an interruption of therapy at doses higher than the recommended starting dose. However to reduce the possibility of [redacted] Patients should be titrated back to their maintenance dose as described in DOSAGE AND ADMINISTRATION section of the PI. [redacted] post-marketing case of vomiting with esophageal rupture reported to have occurred after reinitiation of treatment at an inappropriate single dose of 4.5 mg following an interruption of treatment of for 8 weeks. [redacted]

9.3 Teleconference With Sponsor

At a teleconference today with the sponsor the following was conveyed by Dr R. Katz, Division Director

- The single case of esophageal rupture should be described in the WARNINGS section of the label [redacted]
- Additional text should be incorporated into the PRECAUTIONS: Information For Patients And Caregivers section of the label to make that section consistent with statements in the WARNINGS and DOSAGE AND ADMINISTRATION sections
- The choice of a [redacted] of dosing interruption beyond which re-titration from a starting dose of 1.5 mg b.i.d has been recommended is arbitrary and not supported by the sponsor's analysis which in any case is based upon a relatively small sample. The sponsor will substitute "several days" for [redacted]
- The phrase [redacted] should be deleted from the Dear Doctor letter.
- It would be best if the Dear Doctor letter mentioned the event that initiated the letter (i.e., esophageal rupture after repeated vomiting) [redacted]

The sponsor was asked to submit a revised label and Dear Doctor letter shortly

Ranjit B. Mani, MD

10. Addendum # 2; December 1, 2000

In a submission dated 11/29/00 which was received by fax today the sponsor has responded to the teleconference of November 14, 2000. Changes have been made to both the labeling and Dear Doctor letter

10.1 Changes To Labeling

Changes to the original approved labeling are highlighted in blue, except that deleted sections of the original labeling are highlighted. Changes made since the last teleconference with the sponsor are either underlined (for additions) or struck through in blue (for deletions).

10.1.1 WARNINGS Section

Gastrointestinal Adverse Reactions:

EXELON® 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 several days, with the lowest daily dose (see DOSAGE AND ADMINISTRATION) to reduce the possibility of severe vomiting and its potentially serious sequelae

10.1.2 PRECAUTIONS: Information For Patients And Caregivers Subsection:

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.

10.1.3 ADVERSE REACTIONS Section

Post-Introduction Reports

Voluntary reports of adverse events temporally associated with Exelon® 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

10.1.4 DOSAGE And ADMINISTRATION Section:

The starting dose of EXELON® is 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of two 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, with the lowest daily dose and titrated as described above The maximum dose is 6 mg BID (12 mg/day).

EXELON® should be taken with meals [redacted] in divided doses in the morning and evening

10.2 Dear Doctor Letter

Key paragraphs in this letter are below. Additions made since the last teleconference with the sponsor are highlighted in blue. Deletions are struck through.

"Novartis would like to inform you of recent changes to the [redacted]

[redacted]

There is limited experience related to restarting [redacted] after an interruption [redacted] therapy at doses higher than the recommended starting dose. However to reduce the possibility of

[redacted]

[redacted] Patients should be titrated back to their maintenance dose as described in DOSAGE AND ADMINISTRATION section of the PI. [redacted] post-marketing case of [redacted] with esophageal rupture reported to have occurred after reinitiation of treatment at an inappropriate single dose of 4.5 mg following an interruption of treatment for 8 weeks. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.3 Teleconference With Sponsor; December 1, 2000

The above submission was discussed with the sponsor today after Dr Katz had earlier spoken to Dr R. Temple. The sponsor was told the following:

- [redacted] package insert after the paragraph beginning with the words "nausea and vomiting"
- [redacted]

An alternative approach to the label alone that may be acceptable for the Division is for the following sentence to be altered as follows (additions are highlighted in red)

If treatment is interrupted for [redacted] several days [redacted] with the lowest daily dose (see DOSAGE AND

ADMINISTRATION) to reduce the possibility of severe vomiting and its potentially serious sequelae

The sponsor's formal proposal is to be forwarded to us shortly.

10.4 Meeting With Sponsor; December 7, 2000

A meeting was held with the sponsor today at which Dr R. Temple was present. A further formal submission was not received prior to the presentation. The following were the salient items conveyed to the sponsor.

- A brief description of the above case of esophageal rupture should be in the WARNINGS section of the label
- While the Division and Dr Temple favor the mailing of the Dear Doctor letter

Ranjit B. Mani, MD

11. Addendum; December 12, 2000

In a submission dated December 11, 2000 the sponsor has done the following:

- Provided draft labeling
-
- Provided the text of the Dear Doctor letter

11.1 Draft Labeling

The relevant sections of the label proposed by the sponsor read as follows. Additions to the original draft labeling (i.e., that contained in the approval letter) are underlined. Deletions from the original text are highlighted using the strikethrough feature.

11.1.1 WARNINGS

Gastrointestinal Adverse Reactions:

EXELON® 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 several days, lowest daily dose (see DOSAGE AND ADMINISTRATION) to reduce the possibility of severe vomiting and its potentially serious sequelae (e.g., one post-marketing 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: .....

11.1.2 PRECAUTIONS: Information For Patients And Caregivers Subsection:

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.

11.1.3 ADVERSE REACTIONS Section

Post-Introduction Reports
Voluntary reports of adverse events temporally associated with Exelon® 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

11.1.4 DOSAGE And ADMINISTRATION Section:

The dosage of EXELON® shown to be effective in controlled clinical trials is 6-12 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 [redacted] starting dose of EXELON® is 1.5 mg twice a day. If this dose is well tolerated, after a minimum of two weeks of treatment, the dose may be increased to 3 mg [redacted] 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*. The maximum dose is 6 mg BID (12 mg/day).

EXELON® should be taken with [redacted] meals in divided doses in the morning and evening

*Reviewer's note: [redacted]

11.2 Label For Dear Doctor Letter

The sponsor has proposed an [redacted] as opposed to an [redacted] The [redacted]

[redacted]

11.3 Dear Doctor Letter

The text of the Dear Doctor letter is unchanged from the last version and the key paragraphs read as follows

"Novartis would like to inform you of recent changes to the [redacted]

There is limited experience related to restarting [redacted] after an interruption of therapy at doses higher than the recommended starting dose. However to reduce the possibility of [redacted] lowest daily dose [redacted] their maintenance dose as described in DOSAGE AND ADMINISTRATION section of the PI. [redacted], post-marketing case of [redacted] with esophageal rupture reported to have occurred after reinitiation of treatment at an inappropriate single dose of 4.5 mg following an interruption of treatment for 8 weeks. [redacted]

[redacted]

12. Addendum; December 19, 2000

An internal Divisional meeting was held today at which Drs R. Temple and L. Stockbridge (of DDMAC) were present.

At the meeting:

- The text of the Dear Doctor letter and label were modified
- It was decided to recommend to the sponsor that the Dear Doctor letter be sent out under the [redacted]

12.1 Label

The sections of the label that were modified today are as follows. They contain the final text as formulated today

12.1.1 WARNINGS

Gastrointestinal Adverse Reactions

Exelon (rivastigmine tartrate) 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 post-marketing report of severe vomiting with esophageal rupture following inappropriate reinitiation of treatment with a 4.5 mg dose after 8 weeks of treatment interruption).

12.1.2 DOSAGE AND ADMINISTRATION

The dosage of Exelon (rivastigmine tartrate) shown to be effective in controlled clinical trials is 6-12 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 Exelon is 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of two 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).

12.2 Dear Doctor Letter

The Dear Doctor letter is to read as follows:

Dear Health Care Provider:

Novartis would like to inform you of recent changes to the WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATIONS sections of the prescribing information (PI) for Exelon. These changes provide guidelines for reinitiating therapy in patients who have interrupted treatment with Exelon

There is limited experience related to restarting Exelon after an interruption in therapy at doses higher than the recommended starting dose. However, to reduce the possibility of serious vomiting , treatment should be with the lowest daily dose After reinitiating therapy, patients should be titrated back to

their maintenance dose as described in the DOSAGE AND ADMINISTRATION section of the PI. [redacted] There has been one [redacted] post-marketing case of [redacted] with esophageal rupture reported to have occurred after reinitiating of treatment at an inappropriate single dose of 4.5 mg following an interruption of treatment for eight weeks.[1]

the remainder of the letter remains as proposed

14. Addendum: Teleconference With Sponsor; 12/20/00

A teleconference was held with the sponsor today. Prior to the teleconference the above modified label and Dear Doctor letter were conveyed to the sponsor by fax.

At the teleconference it was agreed that

- No further modifications to the label were needed
- The Dear Doctor letter should be modified further; the final version of this letter is below

14.1 Dear Doctor Letter

[redacted]

Dear Health Care Provider:

Novartis would like to inform you of recent changes to the WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections of the prescribing information (PI) for Exelon. These changes provide guidelines for reinitiating therapy in patients who have interrupted treatment with Exelon to reduce the risk of severe vomiting.

There is limited experience related to restarting Exelon after an interruption in therapy at doses higher than the recommended starting dose. However, to reduce the possibility of severe vomiting in patients who have interrupted Exelon therapy for longer than several days, treatment should be reinitiated with the lowest daily dose. After reinitiating therapy, patients should be titrated back to their maintenance dose as described in the DOSAGE AND ADMINISTRATION section of the PI. There has been one post-marketing case of severe vomiting with esophageal rupture reported to have occurred after reinitiation of treatment at an inappropriate single dose of 4.5 mg following an interruption of treatment for eight weeks.[1]

Novartis is committed to providing you with the most current product information available for the management of patients receiving Exelon. You can further our understanding of adverse events by reporting them.

Healthcare professionals should report all serious adverse events suspected to be associated with use of Exelon to Novartis Pharmaceuticals Corporation, 59 Route 10, East Hanover, New Jersey 07936 by phone (888) NOW-NOVARTIS or (888-669-6682) or the internet at http://www.novartis.com.

Alternatively, this information may be reported to the FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by fax 1-800-FDA-0178, by mail using the Form 3500 at MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20857; or the internet at http://www.accessdata.FDA.gov/scripts/medwatch.

Please note that the next revision of the Physicians' Desk Reference (PDR) will not contain these PI changes; therefore, please see the enclosed revised PI for complete prescribing information. Future and current patients being treated with Exelon should be fully informed of the above information.

Sincerely,

Alan L. Bess, M.D.
Vice President
Clinical Safety & Epidemiology

Stephen R. Cunningham, M.D., FRCP, FFPM
Vice President
Medical Affairs

Babic T, et al. Spontaneous rupture of oesophagus (Boerhaave's syndrome) related to rivastigmine [letter]. Age Aging, 2000, Jul 29(4):370-1

_____
Ranjit B. Mani, MD
Medical Reviewer

J. Feeney, M.D. _____

rbm 12/21/00
cc:
HFD-120
NDA 20823/ 21025
Nighswander

/s/

Ranjit Mani
1/1/01 01:40:18 PM
MEDICAL OFFICER

You have already signed off on this review

John Feeney
1/18/01 03:49:30 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-823/S-003
21-025/S-003

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-823 /S-003
NDA 21-025 /S-003

Novartis Pharmaceuticals Corporation
Attention: James T. Rawls, Pharm.D.
59 Route 10
East Hanover, NJ 07936-1080

Dear Dr. Rawls:

We acknowledge receipt of the following submissions containing final printed labeling in response to our January 5, 2001 letter approving your supplemental new drug applications for Exelon® (rivastigmine tartrate) capsules and oral solution.

NDA 20-823/S-003	February 23, 2001
NDA 21-025/S-003	May 10, 2001

We have reviewed the labeling that you submitted in accordance with our January 5, 2001 letter and we find it acceptable.

If you have any questions, call Robbin Nighswander, Supervisory Regulatory Project Manager, at (301) 594-5531.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
7/25/01 07:54:29 AM

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date of Review: July 24, 2001
Drug: Exelon Capsules (NDA 20-823)
Exelon Solution (NDA 21-025)
Sponsor: Novartis Pharmaceuticals
Supplements:

NDA 20-823/SLR-003
submitted on November 3, 2000
approved on January 5, 2001
FPL submitted February 23, 2001

NDA 21-025/SLR-003
submitted on November 3, 2000
approved on January 5, 2001
FPL submitted May 10, 2001

Note of interest:

- These supplemental applications were approved based on the capsule application "draft" labeling. The firm was asked to make similar revisions to the oral solution labeling and to submit FPL for each product prior to use of the labeling.

REVIEW

20-823/SLR-003 "FA" submission providing FPL after approval
21-025/SLR-003 "FA" submission providing FPL after approval

Dated: 2-23-2001 for the capsule
5-10-2001 for the oral solution
CBE: Yes
Label Code: Capsule T2000-74
89007403 (January, 2001)
Oral Solution T2001-01
89009402 (January, 2001)

These "Changes Being Effected" supplemental new drug applications were prompted by a post-marketing report of esophageal rupture after severe vomiting and provide for revision of the WARNINGS, PRECAUTIONS and DOSAGE and ADMINISTRATION sections of the package insert to provide guidelines for reinitiating therapy in patients who have interrupted treatment with Exelon to reduce the risk of severe vomiting. Additionally, the ADVERSE REACTIONS section has been revised to include a report of a case of Stevens-Johnson syndrome.

The firm notes in the cover letters to their submissions that additional minor editorial changes throughout the package inserts have been made. See table of changes below:

Prescribing Information (PI) Section	Description of Change
Throughout PI	Changed "3.0 mg" and 6.0 mg" to "3 mg" and "6 mg"
DESCRIPTION – 2nd paragraph, 2nd sentence	Changed "silicone" to "silicon"
CLINICAL PHARMACOLOGY – Figure 3, X-axis	Changed "CIBIC" to "CIBIC-Plus"
Carcinogenesis, Mutagenesis, Impairment of Fertility – 1st paragraph, 2nd sentence	Changed "12 mg per day" to "12 mg/day"
ADVERSE REACTIONS – Gastrointestinal System	Changed "gastrosophageal reflux" to "gastroesophageal reflux"
ADVERSE REACTIONS – Metabolic and Nutritional Disorders	Changed "hyperliperna" to "hyperlipemia"

CONCLUSIONS

1. The FPL only provides for the changes in the approval letter dated January 5, 2001 with the exception of the additional "minor" changes noted in the cover letters. These "minor" changes are acceptable.

An Acknowledge and Retain letter can issue advising the firm the FPL is acceptable.

Robbin Nighswander, R.Ph., M.S.
Supervisory Regulatory Project Manager

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

/s/

Robbin Nighswander
7/24/01 05:39:00 PM
CSO