NOVARTIS

Exelon®

Hard capsules.

Brain-selective cholinesterase inhibitor.

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Hard capsules

Active substance

Each Exelon hard gelatin capsule contains rivastigmine hydrogen tartrate corresponding to 1.5, 3.0, 4.5 or 6.0 mg rivastigmine base.

Certain dosage strengths may not be available in all countries.

Excipients

Capsules

Capsule Content: microcrystalline cellulose; magnesium stearate; hypromellose; silica, colloidal anhydrous.

Capsules Shell: gelatin; titanium dioxide (E 171); iron oxide, yellow (E 172); printing ink, based on iron oxide, red (E 172) and shellac.

Pharmaceutical formulations may vary between countries.

INDICATIONS

Treatment of patients with mild to moderately severe dementia of the Alzheimer type, also termed probable Alzheimer's Disease or Alzheimer's Disease.

Treatment of patients with mild to moderately severe dementia associated with Parkinson's disease.

DOSAGE REGIMEN AND ADMINISTRATION

Administration

Dosage regimen

Initial dose

1.5 mg twice a day.

Dose titration

The starting dose 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 twice a day. Subsequent increases to 4.5 mg and then 6 mg twice a day should also be based on good tolerability of the current dose and may be considered after a minimum of two weeks' treatment at that dose level.

If adverse effects (e.g., nausea, vomiting, abdominal pain, or loss of appetite) or weight decrease are observed during treatment, these may respond to omitting one or more doses. If adverse effects persist, the daily dose should be reduced to the previous well-tolerated dose.

Maintenance dose

1.5 mg to 6 mg twice a day; to achieve maximum therapeutic benefit patients should be maintained on their highest well-tolerated dose.

Recommended maximum daily dose

6 mg twice a day.

Re-initiation of therapy

The incidence and severity of adverse events are generally increased with higher doses.

If treatment is interrupted for longer than three days, treatment should be re-initiated with the lowest daily dose and titrated as described above.

Special populations

Pediatric patients (below 18 years)

The use of Exelon in pediatric patients has not been studied and is therefore not recommended.

Method of administration

Exelon hard capsules or Exelon oral solution should be administered twice a day, with morning and evening meals.

Renal impairment or hepatic impairment

No dose adjustment is necessary in patients with renal or hepatic impairment. However, due to increased exposure in moderate renal and mild to moderate hepatic impairment, dosing recommendations to titrate according to individual tolerability should be closely followed as patients with clinically significant renal or hepatic impairment might experience more dose

dependent adverse reactions. Patients with severe hepatic impairment have not been studied (see sections CLINICAL PHARMACOLOGY – Special population and WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS

The use of Exelon is contraindicated in patients with:

- Known hypersensitivity to rivastigmine, to other carbamate derivatives or to the excipients of the formulation (see section DESCRIPTION AND COMPOSITION-Excipients)
- previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine transdermal patch (see section WARNINGS AND PRECAUTIONS – Skin reactions)

WARNINGS AND PRECAUTIONS

Treatment should always be started at a dose of 1.5 mg twice daily and titrated to the patient's maintenance dose. If treatment is interrupted for longer than three days, treatment should be re-initiated with the lowest daily dose to reduce the possibility of adverse reactions (e.g., severe vomiting) (see section DOSAGE REGIMEN AND ADMINISTRATION).

Gastrointestinal disorders such as nausea, vomiting and diarrhoea may occur when initiating treatment and/or increasing the dose. They may respond to a dose reduction. In other cases, use of Exelon has been discontinued. Patients who show signs or symptoms of dehydration resulting from prolonged vomiting or diarrhea can be managed with intravenous fluids and dose reduction or discontinuation if recognized and treated promptly. Dehydration can be associated with serious outcomes (see section ADVERSE DRUG REACTIONS).

Patients with Alzheimer's disease may lose weight while taking cholinesterase inhibitors, including rivastigmine. The patient's weight should be monitored during therapy with Exelon.

Patients with body weight below 50 kg may experience more adverse events and may be more likely to discontinue due to adverse events.

As with other cholinomimetics, care must be taken when using Exelon in patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block) (see section ADVERSE DRUG REACTIONS).

Cholinergic stimulation may cause increased gastric acid secretion and may exacerbate urinary obstruction and seizures. Caution is recommended in treating patients predisposed to such conditions.

Like other cholinomimetics, Exelon should be used with caution in patients with a history of asthma or obstructive pulmonary disease.

Like other cholinomimetics, rivastigmine may induce or exacerbate extrapyramidal symptoms. In patients with dementia associated with Parkinson's disease who were treated with Exelon capsules, worsening of parkinsonian symptoms, particularly tremor, has been observed (see section ADVERSE DRUG REACTIONS).

QT prolongation and torsade de pointes

Electrocardiogram QT prolongation may occur in patients treated with certain cholinesterase inhibitor products including rivastigmine. Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, hypokalemia or hypomagnesemia, personal or family history of QT prolongation, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes. Clinical monitoring may also be required (see section 8 Interactions).

Skin reactions

In patients who develop application site reactions suggestive of allergic contact dermatitis to Exelon 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.

Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g., increasing erythema, edema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued (see section CONTRAINDICATIONS).

There have been isolated post-marketing reports of patients experiencing allergic dermatitis (disseminated) when administered rivastigmine irrespective of the route of administration (oral, transdermal). In these cases, treatment should be discontinued (see section CONTRAINDICATIONS). Patients and caregivers should be instructed accordingly.

Special populations

Patients with clinically significant renal or hepatic impairment may experience more adverse reactions. Dosing recommendations to titrate according to individual tolerability should be closely followed (see section DOSAGE REGIMEN AND ADMINISTRATION). Patients with severe hepatic impairment have not been studied, however, Exelon capsules may be used in this patient population provided close monitoring is exercized.**Driving and using machines**

Alzheimer's and Parkinson's disease dementia may cause gradual impairment of driving performance or compromise the ability to use machinery. Rivastigmine may induce dizziness and somnolence, mainly when initiating treatment or increasing the dose. Therefore, in patients with dementia treated with Exelon, the ability to continue driving or operating complex machines should be routinely evaluated by the treating physician.

ADVERSE DRUG REACTIONS

The most commonly reported adverse drug reactions are gastrointestinal including nausea (38%) and vomiting (23%), especially during titration. Female patients in clinical studies were found to be more susceptible to gastrointestinal adverse drug reactions and weight loss.

Adverse drug reactions from clinical trials in Table 1 and 2 are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Table 1 Adverse drug reactions accumulated in patients with Alzheimer's dementia treated with Exelon hard capsules

Infections and infestations	
Very rare:	Urinary infection
Psychiatric disorders	
Common:	Agitation, confusion, nightmares, anxiety
Uncommon:	Insomnia, depression
Very rare:	Hallucinations
Nervous system disorders	
Very common:	Dizziness
Common:	Headache, somnolence, tremor
Uncommon:	Syncope
Rare:	Seizures
Cardiac disorders	
Rare:	Angina pectoris, myocardial infarction
Very rare:	Cardiac arrhythmia (e.g., bradycardia, atrio-ventricular block, atrial fibrillation, and tachycardia)
Vascular disorders	
Very rare:	Hypertension
Gastrointestinal disorders	
Very common:	Nausea, vomiting, diarrhoea, loss of appetite
Common:	Abdominal pain and dyspepsia
Rare:	Gastric and duodenal ulcers
Very rare:	Gastrointestinal haemorrhage, pancreatitis, severe vomiting associated with oesophageal rupture
Hepatobiliary disorders	
Uncommon:	Abnormal hepatic function tests
Skin and subcutaneous tissue disorders	
Common:	Hyperhydrosis
Rare:	Rash, pruritus
General disorders and administration site conditions	
Common:	Fatigue and asthenia, malaise

Uncommon:	Fall
Investigations	
Common:	Weight loss

Table 2 Adverse drug reactions reported during a 24-week period in clinical studies conducted in patients with dementia associated with Parkinson's disease treated with Exelon hard capsules

Adverse drug reactions		**Study B 2315**	**Study B 2311**	
		Exelon capsules n (%)	Exelon capsules n (%)	Placebo n (%)
Total patients studied		294 (100)	362 (100)	179 (100)
Metabolism and nutritional disorders				
Common:	Decreased appetite	14 (4.8)	28 (7.7)	8 (4.5)
Common:	Dehydration	2 (0.7)	8 (2.2)	2 (1.1)
Psychiatric disorders				
Common:	Anxiety	13 (4.4)	11 (3.0)	1 (0.6)
Common:	Insomnia	7 (2.4)	10 (2.8)	4 (2.2)
Common:	Restlessness	1 (0.3)	10 (2.8)	3 (1.7)
Nervous system disorders				
Very common:	Tremor	67 (22.8)	37 (10.2)	7 (3.9)
Common:	Dizziness	24 (8.2)	20 (5.5)	2 (1.1)
Common:	Somnolence	18 (6.1)	13 (3.6)	5 (2.8)
Common:	Headache	12 (4.1)	15 (4.1)	5 (2.8)
Common:	Parkinson's disease (worsening)	*	12 (3.3)	2 (1.1)
Common:	Bradykinesia	9 (3.1)	9 (2.5)	3 (1.7)
Common:	Dyskinesia	10 (3.4)	5 (1.4)	1 (0.6)
Common:	Cogwheel rigidity	9 (3.1)	1 (0.3)	0 (0.0)
Common:	Hypokinesia	7 (2.4)	1 (0.3)	0 (0.0)
Uncommon:	Dystonia	0 (0.0)	3 (0.8)	1 (0.6)
Cardiac disorders				
Common:	Bradycardia	2 (0.7)	5 (1.4)	1 (0.6)
Uncommon:	Atrial Fibrillation	1 (0.3)	2 (0.6)	0 (0.0)
Uncommon:	Atrioventricular block	1 (0.3)	0 (0.0)	1 (0.6)
Gastrointestinal disorders				
Very common:	Nausea	113 (38.4)	105 (29.0)	20 (11.2)
Very common:	Vomiting	38 (12.9)	60 (16.6)	3 (1.7)
Common:	Diarrhoea	24 (8.2)	26 (7.2)	8 (4.5)
Common:	Abdominal pain and dyspepsia	12 (4.1)	15 (4.1)	1 (0.6)
Common:	Salivary hypersecretion	6 (2.0)	5 (1.4)	0 (0.0)
Skin and subcutaneous tissue disorders				
Common:	Sweating increased	6 (2.0)	8 (2.2)	1 (0.6)
General disorders and administration site conditions				

Very Common:	Fall	29 (9.9)	21 (5.8)	11 (6.1)
Common:	Fatigue	16 (5.4)	14 (3.9)	5 (2.8)
	Asthenia	11 (3.7)	6 (1.7)	2 (1.1)
Common:	Gait disturbance	0 (0.0)	6 (1.7)	0 (0.0)

* Worsening of Parkinson's disease in the study 2315 was assessed by reported pre-identified AEs (tremor, bradykinesia, cogwheel rigidity, fall), each of them listed with corresponding frequencies.

Additional adverse reactions observed during a 76-week prospective, open-label study in patients with dementia associated with Parkinson's disease treated with Exelon capsules: hypertension, hypotension (common).

The following additional adverse drug reactions have been reported in a clinical study in patients with dementia associated with Parkinson's disease treated with Exelon Patch: agitation, depression (common).

Additional adverse drug reactions from post-marketing spontaneous reports (frequency not known)

The following additional adverse drug reactions have been identified with Exelon hard capsules based on post-marketing spontaneous reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Frequency not known: dehydration, aggression, restlessness, extrapyramidal symptoms in patients with Alzheimer's dementia, sick sinus syndrome, hepatitis, Allergic dermatitis (disseminated).

Additional adverse drug reactions which have been reported with Exelon Patch

Common: urinary incontinence

Uncommon: cerebrovascular accident, delirium, psychomotor hyperactivity

Rarely reported: erythema, urticaria, blister, allergic dermatitis (localized)

Information from clinical trials in patients with dementia associated with Parkinson's disease

Table 3 lists the number and percentage of patients from the specific 24-week clinical study conducted with Exelon in patients with dementia associated with Parkinson's disease with pre-defined events that may reflect worsening of Parkinson's disease.

Table 3 Pre-defined events that may reflect worsening of Parkinson's disease in patients with dementia associated with Parkinson's disease (Study B2311)

	Exelon n (%)	Placebo n (%)
Total patients studied	362 (100)	179 (100)
Total patients with pre-defined AEs	99 (27.3)	28 (15.6)
Tremor	37 (10.2)	7 (3.9)
Fall	21 (5.8)	11 (6.1)
Parkinson's disease (worsening)	12 (3.3)	2 (1.1)
Salivary hypersecretion	5 (1.4)	0
Dyskinesia	5 (1.4)	1 (0.6)
Parkinsonism	8 (2.2)	1 (0.6)
Hypokinesia	1 (0.3)	0
Movement disorder	1 (0.3)	0
Bradykinesia	9 (2.5)	3 (1.7)
Dystonia	3 (0.8)	1 (0.6)
Gait abnormality	5 (1.4)	0
Muscle rigidity	1 (0.3)	0
Balance disorder	3 (0.8)	2 (1.1)
Musculoskeletal stiffness	3 (0.8)	0
Rigors	1 (0.3)	0
Motor dysfunction	1 (0.3)	0

INTERACTIONS

Rivastigmine is metabolized mainly through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Thus, no pharmacokinetic interactions are anticipated with other drugs metabolized by these enzymes.

Anticipated interactions resulting in a concomitant use not recommended

Metoclopramide

Considering the possibility of an additive extra-pyramidal effect the concomitant use of metoclopramide and rivastigmine is not recommended.

Drugs acting on cholinergic system

In view of its pharmacodynamic effects, rivastigmine should not be given concomitantly with other cholinomimetic drugs due to possible additive effect. Rivastigmine might also interfere with the activity of anticholinergic medications (e.g., oxybutynin, tolterodine).

Succinylcholine-type muscle relaxants

As a cholinesterase inhibitor, rivastigmine may exaggerate the effects of succinylcholine-type muscle relaxants during anaesthesia.

Anticipated interactions to be considered

Medicinal products known to prolong the QT interval

Caution is advised when rivastigmine is used in combination with other medicinal products known to prolong the QT interval (including but not limited to quinidine, amiodarone, pimozide, halofantrine, cisapride, citalopram, mizolastin, moxifloxacin, erythromycin). Clinical monitoring may also be required (see section 6 Warnings and precautions).

Observed interactions to be considered

Beta-blockers

Additive effects leading to bradycardia (which may result in syncope) have been reported with the combined use of various beta-blockers (including atenolol) and rivastigmine. Cardio-selective beta-blockers are expected to be associated with the greatest risk, but reports have also been received in patients using other beta-blockers.

Nicotine

A population pharmacokinetic analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% in patients with Alzheimer's dementia (n=75 smokers and 549 non-smokers) following rivastigmine oral capsule doses of up to 12 mg/day.

Interactions with commonly used concomitant drugs

No pharmacokinetic interaction was observed between oral rivastigmine 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. No untoward effects on cardiac conduction were observed following concomitant administration of digoxin and rivastigmine.

Concomitant administration of rivastigmine with commonly prescribed medications, such as antacids, antiemetics, antidiabetics, centrally acting antihypertensives, calcium channel blockers, inotropic drugs, antianginals, non-steroidal anti-inflammatory drugs, oestrogens,

analgesics, benzodiazepines, and antihistamines, was not associated with an alteration in the kinetics of rivastigmine, or an increased risk of clinically relevant untoward effects.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

The safety of Exelon in human pregnancy has not been established. In pregnant animals, rivastigmine and/or metabolites crossed the placenta. It is not known if this occurs in humans. In animal studies, rivastigmine was not teratogenic. Exelon should only be given to pregnant women if the potential benefit outweighs the potential risk for the fetus.

Animal data

Embryo-fetal toxicity studies in pregnant rats and rabbits with oral dose levels up to 2.3 mg base/kg/day revealed no evidence of teratogenic potential for rivastigmine. In pre- and post-natal studies, there was no evidence of adverse effects of rivastigmine on fertility, reproductive performance or in utero or postnatal growth and development in rats at dose levels up to 1.1 mg base/kg/day.

LactationIt is not known if Exelon is transferred into human milk. In animals, rivastigmine and/or metabolites were transferred into breast milk. Patients on Exelon should therefore not breast-feed.

Females and males of reproductive potential

There is no information available on the effects of rivastigmine in women of child-bearing potential.

Infertility

There is no information available on the effect of rivastigmine on human fertility. In male and female rats, no adverse effects of rivastigmine were observed on fertility or reproductive performance of either the parents or their offspring.

OVERDOSAGE

Symptoms

Most cases of accidental overdosage have not been associated with any clinical signs or symptoms and almost all the patients concerned continued Exelon treatment. Where symptoms have occurred, they have included nausea, vomiting, diarrhea, abdominal pain,

dizziness, tremor, headache, somnolence, bradycardia, confusional state, hyperhidrosis, hypertension, hallucinations, and malaise. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, and convulsions. Muscle weakness is a possibility and may result in death if respiratory muscles are involved. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur.

Fatal outcome has been rarely reported with rivastigmine overdose and the relationship to rivastigmine was unclear. Symptoms of overdose and outcome vary from patient to patient and the severity of the outcome is not predictably related to the amount of the overdose.

Treatment

As rivastigmine has a plasma half-life of about 1 hour and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose no further dose of Exelon should be administered for the next 24 hours. In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. Symptomatic treatment for other adverse events should be given as necessary.

In massive overdose, atropine can be used. An initial dose of 0.03 mg/kg i.v. atropine sulfate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: brain-selective cholinesterase inhibitor; ATC-code: N06DA03.

Mechanism of action/ Pharmacodynamic properties (PD)

Pathological changes in dementia such as Alzheimer's Disease involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are known to be involved in attention, learning and memory and other cognitive processes. Rivastigmine, a brain-selective acetyl- and butyryl-cholinesterase inhibitor of the carbamate type, is thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurons. Data from animal studies indicate that rivastigmine selectively increases the availability of acetylcholine in the cortex and hippocampus. Thus, Exelon may have an ameliorative effect on cholinergic-mediated cognitive deficits associated with Alzheimer's Disease and with Parkinson's disease. In addition, there is some evidence that cholinesterase inhibition could slow the formation of amyloidogenic beta-amyloid-precursor protein (APP) fragments, and thus of amyloid plaques, which are one of the main pathological features of Alzheimer's Disease.

Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes. In healthy young men, an oral 3.0 mg dose decreases acetylcholinesterase (AChE) activity in cerebro spinal fluid (CSF) by approximately 40%

within the first 1.5 hours after administration. Activity of the enzyme returns to baseline levels about 9 hours after the maximum inhibitory effect has been achieved. Butyrylcholinesterase (BuChE) activity in CSF was transiently inhibited and was no longer different from baseline after 3.6 hours in healthy young volunteers. In patients with Alzheimer's Disease (AD), inhibition of acetylcholinesterase in CSF by rivastigmine was dose-dependent up to 6 mg given twice daily, the highest dose tested. Inhibition of BuChE activity in CSF of AD patients by rivastigmine was similar to that of AchE, with a change from baseline of more than 60% after 6 mg given twice daily. The effect of rivastigmine on AChE and BuChE activity in CSF was sustained after 12 months administration, the longest time studied. Statistically significant correlations were found between the degree of inhibition by rivastigmine of AChE and BuChE in the CSF and changes on a compound measure of cognitive performance in AD patients; however, only BuChE inhibition in CSF was significantly and consistently correlated with improvements in speed-, attention- and memory-related subtests.

Pharmacokinetics properties (PK)

Absorption

Rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. As a consequence of the drug's interaction with its target enzyme, the increase in bioavailability is about 1.5-fold greater than that expected from the increase in dose. Absolute bioavailability after a 3 mg dose is about 36%. Administration of rivastigmine capsules with food delays absorption (t_{max}) by 90 min and lowers C_{max} and increases AUC by approximately 30%.

Distribution

Rivastigmine is weakly bound to plasma proteins (approximately 40%). Rivastigmine distributes equally between blood and plasma with a blood-to-plasma partition ratio of 0.9 at concentrations ranging from 1 to 400 ng/mL.It readily crosses the blood brain barrier reaching peak concentrations in 1 to 4 hours, and with a cerebrospinal fluid-to-plasma AUC ratio of 40%. Rivastigmine has a volume of distribution after iv dosing in the range of 1.8-2.7 L/kg.

Metabolism

Rivastigmine is rapidly and extensively metabolized (half-life in plasma approximately 1 hour), primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. *In vitro,* this metabolite shows minimal inhibition of acetylcholinesterase (<10%). Based on *in vitro* studies, no pharmacokinetic drug interactions are expected with drugs metabolized by the following cytochrome isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6. Based on evidence from animal studies, the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Consistent with these observations is the finding that no drug interactions relating to cytochrome P450 have been observed in humans (see section INTERACTIONS).

Elimination

Unchanged rivastigmine is not found in the urine; renal excretion of the metabolites is the major route of elimination. Following administration of ^{14}C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's Disease.

Special population

Elderly subjects

In a study to assess the effect of age on the pharmacokinetics of 1 and 2.5 mg oral rivastigmine, plasma concentrations of rivastigmine tended to be higher in the elderly (n=24, aged 61 to 71 years) as compared to young subjects (n=24, aged 19 to 40 years) after the 1 mg dose. This difference was more pronounced with the higher dose (2.5 mg) at which rivastigmine plasma concentrations were 30% greater in the healthy elderly than in healthy young subjects. Plasma levels of the decarbamylated phenolic metabolite were not substantially affected by age. studies in Alzheimer patients aged between 50 and 92 years, however showed no change in rivastigmine bioavailability with age.

Renal impairment

Plasma levels of rivastigmine were reported not to differ significantly between patients with severe renal impairment (n=10, glomerula filtration rate (GFR) <10 mL/minute) and control subjects (n=10, GFR ≥60 mL/min) given a single oral dose of 3 mg. Clearance of rivastigmine was 4.8 L/min and 6.9 L/min in patients and healthy subjects, respectively. However, in moderately impaired renal patients (n=8, GFR=10 to 50 mL/min), peak plasma concentrations of rivastigmine were increased by almost 2.5 fold and overall plasma levels (AUC) of the decarbamylated phenolic metabolite were increased by approximately 50%. Clearance of rivastigmine was 1.7 L/min. The reason for this discrepancy between severely and moderately impaired renal patients is unclear. (See section DOSAGE REGIMEN AND ADMINISTRATION and section WARNINGS AND PRECAUTIONS).

Hepatic impairment

After oral administration, the C_{max} of rivastigmine was approximately 60% higher and the AUC more than twice as high in subjects with mild to moderate hepatic impairment compared to healthy subjects. Following a single 3-mg dose or multiple 6-mg twice a day doses, the mean oral clearance of rivastigmine was approximately 60 to 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 (n=10, biopsy proven) than in healthy subjects (n=10). (see section DOSAGE REGIMEN AND ADMINISTRATION AND section WARNINGS AND PRECAUTIONS).

CLINICAL STUDIES

Clinical studies in Alzheimer's Dementia

The efficacy of Exelon in the treatment of Alzheimer's Disease has been demonstrated in placebo-controlled studies. The patients involved had an MMSE (Mini-Mental State Examination) of 10 to 24. Results from two pivotal 26-week multicenter studies comparing 1 to 4 mg/day and 6 to 12 mg/day with placebo, as well as pooled analysis of Phase III studies have established that Exelon produces significant improvement in the major domains of cognition, global functioning, and activities of daily living, and in disease severity. Both the low and high dose ranges showed benefit for cognition, global functioning, and disease severity; in addition, the higher dose range produced benefit in activities of daily living.

The following key outcome measures were used in these studies:

Alzheimer's Disease Assessment Scale (ADAS-Cog): a performance-based test system that measures cognitive areas relevant for patients with Alzheimer's Disease such as attention, learning, memory, and language;

Clinician Interview Based Impression of Change-Plus (CIBIC-Plus): a clinician-rated assessment of the patient's global change in the domains of cognition, behaviour, and functioning, incorporating separate patient and caregiver inputs;

Progressive Deterioration Scale (PDS): a caregiver-rated evaluation of the patient's ability to perform activities of daily living such as toileting, washing, eating, and helping with household chores and shopping.

Study results have indicated that onset of efficacy is generally as early as week 12 and is maintained at the end of 6 months of treatment. Patients treated with 6 to 12 mg experienced improvement in cognition, activities of daily living and global functioning, while placebo patients showed deterioration. The effects of Exelon on these measures (e.g., ADAS-Cog difference from placebo 5 points at week 26) indicate a delay in the rate of deterioration of at least 6 months.

Analyses performed to detect those subtests and symptoms of the ADAS-Cog and CIBIC-Plus, respectively, which improved in patients treated with Exelon indicated that all ADAS-Cog subtests (ideational praxis, orientation, test instructions, word recall, language ability and word recognition) and all CIBIC-Plus items, except anxiety, were significantly improved at week 26 with Exelon 6 to 12 mg. Items which improved in at least 15% more Exelon than placebo patients completing treatment included word recall, functioning, agitation, tearfulness or crying, delusions, hallucinations, purposeless and inappropriate activities, and physical threats and/or violence.

Clinical studies in dementia associated with Parkinson's disease

The efficacy of rivastigmine in dementia associated with Parkinson's disease has been demonstrated in a 24-week multi-center, double blind, placebo-controlled core study and its 24-week open-label extension phase. Patients involved in this study had an MMSE (Mini-Mental State Examination) of 10 to 24. Efficacy has been established by the use of two independent scales which were assessed at regular intervals during a 6-month treatment

period as reported in Table 4 below: the ADAS-cog, a measure of cognition and the global measure ADCS-CGIC (Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change).

Table 4 Dementia associated with Parkinson's Disease

Dementia associated with Parkinson's Disease	**ADAS-Cog Exelon**	**ADAS-Cog Placebo**	**ADCS-CGIC Exelon**	**ADCS-CGIC Placebo**
ITT + RDO population	(n=329)	(n=161)	(n=329)	(n=165)
Mean baseline ± SD	23.8 ± 10.2	24.3 ± 10.5	n/a	n/a
Mean change at 24 weeks ± SD	2.1 ± 8.2	-0.7 ± 7.5	3.8 ± 1.4	**4.3** ± 1.5
Adjusted treatment difference	2.88[1]		n/a	
p-value vs placebo	<0.001[1]		0.007[2]	
ITT - LOCF population	(n=287)	(n=154)	(n=289)	(n=158)
Mean baseline ± SD	24.0 ± 10.3	24.5± 10.6	n/a	n/a
Mean change at 24 weeks ± SD	2.5 ± 8.4	-0.8 ± 7.5	3.7 ± 1.4	4.3 ± 1.5
Adjusted treatment difference	3.54[1]		n/a	
p-value vs placebo	<0.001[1]		<0.001[2]	

[1] Based on ANCOVA, with treatment &country as factors and baseline ADAS-cog as a covariate. A positive change indicates improvement.
[2] mean data shown for convenience, categorical analysis done using van Elteren test

ITT: Intention-To-Treat; RDO: Retrieved Drop outs; LOCF: Last Observation Carried Forward.

Although a treatment effect was demonstrated in the overall study population, the data suggested that a larger treatment effect relative to placebo was seen in the subgroup of patients with moderate dementia associated with Parkinson's disease. Similarly a larger treatment effect was observed in those patients with visual hallucinations (see Table 5)

Table 5

Dementia associated with Parkinson's Disease	ADAS-Cog Exelon	ADAS-Cog Placebo	ADAS-Cog Exelon	ADAS-Cog Placebo
	Patients with visual hallucinations		**Patients without visual hallucinations**	
ITT + RDO population	(n=107)	(n=60)	(n=220)	(n=101)
Mean baseline ± SD	25.4 ± 9.9	27.4 ± 10.4	23.1±10.4	22.5±10.1
Mean change at 24 weeks ± SD	1.0 ± 92	-2.1 ± 8.3	2.6 ± 7.6	0.1 ± 6.9
Adjusted treatment difference	4.27[1]		2.09[1]	
p-value versus placebo	0.002[1]		0.015[1]	
	Patients with moderate dementia (MMSE 10-17)		**Patients with mild dementia (MMSE 18-24)**	
ITT + RDO population	(n=87)	(n=44)	(n=237)	(n=115)
Mean baseline ± SD	32.6 ± 10.4	33.7 ± 10.3	20.6 ± 7.9	20.7 ± 7.9
Mean change at 24 weeks ± SD	2.6 ± 9.4	-1.8 ± 7.2	1.9 ± 7.7	-0.2 ± 7.5
Adjusted treatment difference	4.73[1]		2.14	
p-value versus placebo	0.002[1]		0.010[1]	

[1] Based on ANCOVA, with treatment &country as factors and baseline ADAS-cog as a covariate. A positive change indicates improvement.
ITT: Intention-To-Treat; RDO: Retrieved Drop outs

NON-CLINICAL SAFETY DATA

Acute toxicity

The estimated oral LD_{50} values in mice were 5.6 mg base/kg (males) and 13.8 mg base/kg (females). The estimated oral LD_{50} values in rats were 8.1 mg base/kg (males) and 13.8 mg base/kg (females).

Repeated dose toxicity

Studies in rats, mice, dogs, minipigs and monkeys (maximum doses 3.8, 6.3, 2.5 , 6.0 and 6.3 mg-base/kg/day, respectively) revealed evidence of cholinergic stimulation of the central and peripheral nervous systems. In-life tolerability to rivastigmine was variable between species, with the dog as the most sensitive species. No target organ toxicities or clinical

pathology alterations were observed in any species, although gastro-intestinal effects were prominent in dogs.

Mutagenicity

Rivastigmine was not mutagenic in *in vitro* tests for gene mutations and primary DNA damage. In tests for chromosomal damage *in vitro*, a small increase in the number of cells carrying chromosomal aberrations occurred at very high concentrations. However, as there was no evidence of clastogenic activity in the more relevant *in vivo* micronucleus test assessing chromosomal damage, it is most likely that the *in vitro* findings were false positive observations. In addition, the major metabolite NAP226-90 did not induce structural chromosome aberrations in an *in vitro* test indicating that the compound has no genotoxic potential.

Carcinogenicity

No evidence of carcinogenicity was found in studies in mice and rats at the maximum tolerated dose, although the exposure to rivastigmine and its metabolites was lower than the human exposure. When normalised to body surface area, the exposure to rivastigmine and its metabolites was approximately equivalent to the maximum recommended human dose of 12mg/day; however, when compared to the maximum human dose, a multiple of approximately 6-fold was achieved in animals.

Reproductive toxicity

See section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Local tolerance

A mild eye/mucosal irritation potential of rivastigmine was identified in a rabbit study.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Exelon should not be used after the date marked “EXP” on the pack.

Exelon must be kept out of the reach and sight of children.

Country Specific Package Leaflet

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