

New Zealand Data Sheet

EXELON[®] **Rivastigmine** **1.5, 3.0, 4.5 or 6.0 mg capsules**

Qualitative and quantitative composition

Exelon[®] hard capsules contain 1.5, 3.0, 4.5 or 6.0 mg rivastigmine (as the hydrogen tartrate salt).

Excipients

3.0 and 6.0 mg capsules

Gelatin; iron oxide, red (E 172); iron oxide, yellow (E 172); magnesium stearate; methylhydroxypropylcellulose; microcrystalline cellulose; printing ink, based on iron oxide, red (E 172); silica, colloidal anhydrous; titanium dioxide (E 171).

1.5 mg capsules

Gelatin; iron oxide, yellow (E 172); magnesium stearate; methylhydroxypropylcellulose; microcrystalline cellulose; printing ink, based on iron oxide, red (E 172); silica, colloidal anhydrous; titanium dioxide (E 171).

4.5 mg capsules

Gelatin; iron oxide, red (E 172); iron oxide, yellow (E 172); magnesium stearate; methylhydroxypropylcellulose; microcrystalline cellulose; printing ink, based on titanium dioxide (E 171); silica, colloidal anhydrous; titanium dioxide (E 171).

Pharmaceutical form

Hard capsule.

Clinical particulars

Indications

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

Dosage and administration

Administration

Exelon should be administered twice a day, with morning and evening meals.

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 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 several days, treatment should be re-initiated with the lowest daily dose and titrated as described above.

Use in children

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

Use in patients with renal 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 adverse events. Patients with severe liver impairment have not been studied, however, Exelon capsules may be used in this patient population provided close monitoring is exercised (see Warnings and precautions – Special population).

Contraindications

The use of Exelon is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other ingredients of the formulation (see Excipients).

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 several days, treatment should be re-initiated with the lowest daily dose to reduce the possibility of adverse reactions (e.g. severe vomiting) (see Dosage 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 diarrhoea can be managed with iv fluids and dose reduction or discontinuation if recognized and treated promptly. Dehydration can be associated with serious outcomes (see Adverse effects).

Patients with Alzheimer's disease may lose weight whilst 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 Adverse effects).

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.

Special population

Patients with clinically significant renal or hepatic impairment may experience more adverse events. Dosing recommendations to titrate according to individual tolerability should be closely followed (see Dosage and administration). Patients with severe liver impairment have not been studied, however, Exelon capsules or oral solution may be used in this patient population provided close monitoring is exercised.

Interactions

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

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, β -blockers, 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.

In view of its pharmacodynamic effects, rivastigmine should not be given concomitantly with other cholinomimetic drugs and might interfere with the activity of anticholinergic medications.

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

Pregnancy and breast-feeding

Pregnancy

In animal studies, rivastigmine was not teratogenic. However, the safety of Exelon in human pregnancy has not been established, and it should only be given to pregnant women if the potential benefit outweighs the potential risk for the foetus.

Breast-feeding

In animals, rivastigmine and/or metabolites were transferred to the milk. It is not known if Exelon is excreted into human milk, and patients on Exelon should therefore not breast-feed.

Driving and using machines

Alzheimer'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 effects

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.

The following adverse drug reactions, listed below in Table 1, have been accumulated in patients with Alzheimer's dementia treated with Exelon.

Table 1

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), including isolated reports.

Infections and infestations	
Very rare:	Urinary infection
Psychiatric disorders	
Common:	Agitation, confusion, 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
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Skin and subcutaneous tissue disorders

Common:	Hyperhidrosis
Rare:	Rash, pruritis

General disorders and administration site conditions

Common:	Fatigue and asthenia, malaise
Uncommon:	Fall

Investigations

Common:	Weight loss
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Additional adverse drug reactions from post-marketing spontaneous reports

The following additional adverse drug reactions have been identified with Exelon hard capsules or Exelon oral solution 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.

Metabolism and nutrition disorders

Dehydration

Psychiatric disorders

Aggression, restlessness

Cardiac disorders

Sick sinus syndrome

Hepatobiliary disorders

Hepatitis

Additional adverse drug reactions which have been reported with Exelon Patch

Uncommon: cerebrovascular accident, delirium.

Rarely reported: erythema, urticaria, blister, dermatitis allergic.

**Overdose
Symptoms**

Most cases of accidental overdosage have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued Exelon treatment. Where symptoms have occurred, they have included nausea, vomiting, diarrhoea, hypertension and hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur.

Ingestion of 46 mg occurred in one case; following conservative management the patient fully recovered within 24 hours.

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

Mechanism of action/Pharmacodynamics (PD)

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

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. 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.

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 10-24. Results from two pivotal 26-week multicentre studies comparing 1-4 mg/day and 6-12 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 6-12 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 6-12 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.

Pharmacokinetics (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%. Administration of rivastigmine oral solution with food delays absorption (t_{max}) by 74 min and lowers C_{max} by 43% and increases AUC by approximately 9%.

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 metabolised (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 evidence from in vitro and 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 Interaction with other medical products and other forms of interaction).

Elimination

Unchanged rivastigmine is not found in the urine; renal excretion of the metabolites is the major route of elimination. Following administration of ¹⁴C-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 61-71 years) as compared to young subjects (n=24, aged 19-40 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 elderly than in 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=10-50 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 Warnings and precautions – Special population and Dosage and administration.

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 60-65% lower in mild (n=7, Child-Pugh score 5-6) and moderate (n=3, Child-Pugh score 7-9) hepatically impaired patients (n=10, biopsy proven) than in healthy subjects (n=10). These pharmacokinetic changes had no effect on either the incidence or severity of adverse effects. See Warnings and precautions – Special population and Dosage and administration.

Preclinical 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 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 test, it is most likely that the *in vitro* findings were false positive observations.

Carcinogenicity

No evidence of carcinogenicity was found in oral and topical studies in mice and in oral study in rats at the maximum tolerated dose. The exposure to rivastigmine and its major metabolite was approximately equivalent to human exposure with highest doses of rivastigmine capsules and patches.

Reproductive toxicity

Oral studies in pregnant rats and rabbits with dose levels up to 2.3 mg base/kg/day gave no indication of teratogenic potential on the part of rivastigmine. Similarly, there was no evidence of adverse effects of rivastigmine on fertility, reproductive performance or in utero or postnatal growth and development in rats at given dose levels up to 1.1 mg base/kg/day.

Pharmaceutical particulars

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 30°C.

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

Instructions for use, handling and disposal (if appropriate)

Not applicable.

Medicine classification

Prescription Medicine

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