**RIVASTIGMINE**

**Therapeutics**

**Brands**  •  Exelon
*see index for additional brand names*

**Generic?**  Yes

**Class**
• Neuroscience-based Nomenclature:  
  Acetylcholine enzyme inhibitor (ACh-EI)
• Cholinesterase inhibitor (acetylcholinesterase inhibitor and butyrylcholinesterase inhibitor);  
  cognitive enhancer

**Commonly Prescribed for**
(bold for FDA approved)
• Alzheimer disease (mild to moderate)
• Parkinson’s disease dementia (mild to moderate)
• Memory disorders in other conditions
• Mild cognitive impairment

**How the Drug Works**
* Pseudoirreversibly inhibits centrally active acetylcholinesterase (AChE), making more acetylcholine available
* Increased availability of acetylcholine compensates in part for degenerating cholinergic neurons in neocortex that regulate memory
* Inhibits butyrylcholinesterase (BuChE)
* May release growth factors or interfere with amyloid deposition

**How Long Until It Works**
• May take up to 6 weeks before any improvement in baseline memory or behavior is evident
• May take months before any stabilization in degenerative course is evident

**If It Works**
• May improve symptoms and slow progression of disease, but does not reverse the degenerative process

**If It Doesn’t Work**
• Consider adjusting dose, switching to a different cholinesterase inhibitor or adding an appropriate augmenting agent
• Reconsider diagnosis and rule out other conditions such as depression or a dementia other than Alzheimer disease

**Best Augmenting Combos for Partial Response or Treatment Resistance**
* Atypical antipsychotics to reduce behavioral disturbances
* Antidepressants if concomitant depression, apathy, or lack of interest
* Memantine for moderate to severe Alzheimer disease
* Divalproex, carbamazepine, or oxcarbazepine for behavioral disturbances

**Tests**
• None for healthy individuals

**Side Effects**

**How Drug Causes Side Effects**
• Peripheral inhibition of acetylcholinesterase can cause gastrointestinal side effects
• Peripheral inhibition of butyrylcholinesterase can cause gastrointestinal side effects
• Central inhibition of acetylcholinesterase may contribute to nausea, vomiting, weight loss, and sleep disturbances

**Notable Side Effects**
* Nausea, diarrhea, vomiting, appetite loss, weight loss, dyspepsia, increased gastric acid secretion
• Headache, dizziness
• Fatigue, asthenia, sweating

**Life-Threatening or Dangerous Side Effects**
• Rare seizures
• Rare syncope

**Weight Gain**
* Reported but not expected
• Some patients may experience weight loss

**Sedation**
* Reported but not expected

**What to Do About Side Effects**
• Wait
**RIVASTIGMINE (continued)**

- Wait
- Wait
- Use slower dose titration
- Consider lowering dose, switching to a different agent or adding an appropriate augmenting agent

**Best Augmenting Agents for Side Effects**
- Many side effects cannot be improved with an augmenting agent

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### DOSING AND USE

#### Usual Dosage Range
- **Oral:** 6–12 mg/day in 2 doses
- **Transdermal:** 9.5 mg/24 hours once daily

#### Dosage Forms
- Capsule 1.5 mg, 3 mg, 4.5 mg, 6 mg
- Liquid 2 mg/mL – 120 mL bottle
- Transdermal 9 mg/5 cm² (4.6 mg/24 hours), 18 mg/10 cm² (9.5 mg/24 hours), 27 mg/15 cm² (13.3 mg/24 hours)

#### How to Dose
- **Oral:** initial 1.5 mg twice daily; increase by 3 mg every 2 weeks; titrate to tolerability; maximum dose generally 6 mg twice daily
- **Transdermal:** initial 4.6 mg/24 hours; after 4 weeks increase to 9.5 mg/24 hours; maximum recommended dose 13.3 mg/24 hours

#### Dosing Tips
- Incidence of nausea is generally higher during the titration phase than during maintenance treatment
- If restarting treatment after a lapse of several days or more, dose titration should occur as when starting drug for the first time
- Oral doses between 6–12 mg/day have been shown to be more effective than doses between 1–4 mg/day
- Recommended to take oral rivastigmine with food
- Rapid dose titration increases the incidence of gastrointestinal side effects
- For transdermal formulation, dose increases should occur after a minimum of 4 weeks at the previous dose and only if the previous dose was well tolerated
- Transdermal patch should only be applied to dry, intact skin on the upper torso or another area unlikely to rub against tight clothing
- Plasma exposure with transdermal rivastigmine is 20–30% lower when applied to the abdomen or thigh as compared to the upper back, chest, or upper arm
- New application site should be selected for each day; patch should be applied at approximately the same time every day; only one patch should be applied at a time; patches should not be cut; new patch should not be applied to the same spot for at least 14 days
- Avoid touching the exposed (sticky) side of the patch, and after application, wash hands with soap and water; do not touch eyes until after hands have been washed
- Switching from oral formulation to transdermal formulation: patients receiving oral rivastigmine <6 mg/day can switch to 4.6 mg/24 hours transdermal; patients receiving oral rivastigmine 6–12 mg/day can switch to 9.5 mg/24 hours transdermal; apply the first patch on the day following the last oral dose
- Probably best to utilize highest tolerated dose within the usual dosage range
- When switching to another cholinesterase inhibitor, probably best to cross-titrate from one to the other to prevent precipitous decline in function if the patient washes out of one drug entirely

#### Overdose
- Can be lethal; nausea, vomiting, excess salivation, sweating, hypotension, bradycardia, collapse, convulsions, muscle weakness (weakness of respiratory muscles can lead to death)

#### Long-Term Use
- Drug may lose effectiveness in slowing degenerative course of Alzheimer disease after 6 months
- Can be effective in many patients for several years

#### Habit Forming
- No

#### How to Stop
- Taper not necessary
RIVASTIGMINE

SPECIAL POPULATIONS

Renal Impairment
• Dose adjustment not necessary; titrate to point of tolerability

Hepatic Impairment
• Dose adjustment not necessary; titrate to point of tolerability

Cardiac Impairment
• Should be used with caution
• Syncopal episodes have been reported with the use of rivastigmine

Elderly
• Some patients may tolerate lower doses better
• Use of cholinesterase inhibitors may be associated with increased rates of syncope, bradycardia, pacemaker insertion, and hip fracture in older adults with dementia

Children and Adolescents
• Safety and efficacy have not been established

Pregnancy
• Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLRR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
• Controlled studies have not been conducted in pregnant women
• Animal studies do not show adverse effects
• Not recommended for use in pregnant women or women of childbearing potential

Drug Interactions
• Rivastigmine may increase the effects of anesthetics and should be discontinued prior to surgery
• Rivastigmine may interact with anticholinergic agents and the combination may decrease the efficacy of both
• Clearance of rivastigmine may be increased by nicotine
• May have synergistic effect if administered with cholinomimetics (e.g., bethanechol)
• Bradycardia may occur if combined with beta blockers
• Theoretically, could reduce the efficacy of levodopa in Parkinson’s disease
• Not recommended in combination with metoclopramide due to risk of additive extrapyramidal effects
• Not rational to combine with another cholinesterase inhibitor

Other Warnings/Precautions
• May exacerbate asthma or other pulmonary disease
• Increased gastric acid secretion may increase the risk of ulcers
• Bradycardia or heart block may occur in patients with or without cardiac impairment
• Severe vomiting with esophageal rupture may occur if rivastigmine therapy is resumed without retitrating the drug to full dosing
• Individuals with low body weight may be at greater risk for adverse effects
• Certain transdermal patches containing even small traces of aluminum or other metals in the adhesive backing can cause skin burns if worn during MRI, so warn patients taking the transdermal formulation about this possibility and advise them to disclose this information if they need an MRI

Do Not Use
• If there is a proven allergy to rivastigmine or other carbamates

Pharmacokinetics
• Elimination half-life 1–2 hours
• Not hepatically metabolized; no CYP450-mediated pharmacokinetic drug interactions

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• Discontinuation may lead to notable deterioration in memory and behavior, which may not be restored when drug is restarted or another cholinesterase inhibitor is initiated

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Breast Feeding
- Unknown if rivastigmine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
  -* Recommended either to discontinue drug or bottle feed
  -* Rivastigmine is not recommended for use in nursing women

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Theoretically, butyrylcholinesterase inhibition centrally could enhance therapeutic efficacy
- May be useful in some patients who do not respond to or do not tolerate other cholinesterase inhibitors
- Later stages or rapidly progressive Alzheimer disease

Potential Disadvantages
- Theoretically, butyrylcholinesterase inhibition peripherally could enhance side effects

Primary Target Symptoms
- Memory loss in Alzheimer disease
- Behavioral symptoms in Alzheimer disease
- Memory loss in other dementias

Pearls
- Dramatic reversal of symptoms of Alzheimer disease is not generally seen with cholinesterase inhibitors
  -* Can lead to therapeutic nihilism among prescribers and lack of an appropriate trial of a cholinesterase inhibitor
  -* Perhaps only 50% of Alzheimer patients are diagnosed, and only 50% of those diagnosed are treated, and only 50% of those treated are given a cholinesterase inhibitor, and then only for 200 days in a disease that lasts 7–10 years
  -* Must evaluate lack of efficacy and loss of efficacy over months, not weeks
  -* Treats behavioral and psychological symptoms of Alzheimer dementia as well as cognitive symptoms (i.e., especially apathy, disinhibition, delusions, anxiety, lack of cooperation, pacing)

Patients who themselves complain of memory problems may have depression, whereas patients whose spouses or children complain of the patient’s memory problems may have Alzheimer disease
- Treat the patient but ask the caregiver about efficacy
- What you see may depend upon how early you treat
- The first symptoms of Alzheimer disease are generally mood changes; thus, Alzheimer disease may initially be diagnosed as depression
- Women may experience cognitive symptoms in perimenopause as a result of hormonal changes that are not a sign of dementia or Alzheimer disease
- Aggressively treat concomitant symptoms with augmentation (e.g., atypical antipsychotics for agitation, antidepressants for depression)
- If treatment with antidepressants fails to improve apathy and depressed mood in the elderly, it is possible that this represents early Alzheimer disease and a cholinesterase inhibitor like rivastigmine may be helpful
- What to expect from a cholinesterase inhibitor:
  -* Patients do not generally improve dramatically although this can be observed in a significant minority of patients
  -* Onset of behavioral problems and nursing home placement can be delayed
  -* Functional outcomes, including activities of daily living, can be preserved
  -* Caregiver burden and stress can be reduced
  -* Delay in progression in Alzheimer disease is not evidence of disease-modifying actions of cholinesterase inhibition
  -* Cholinesterase inhibitors like rivastigmine depend upon the presence of intact targets for acetylcholine for maximum effectiveness and thus may be most effective in the early stages of Alzheimer disease
  -* The most prominent side effects of rivastigmine are gastrointestinal effects, which are usually mild and transient
  -* May cause more gastrointestinal side effects than some other cholinesterase inhibitors, especially if not slowly titrated
  -* At recommended doses, transdermal formulation may have lower incidence
Suggested Reading


of gastrointestinal side effects than oral formulation
• Use with caution in underweight or frail patients
• Weight loss can be a problem in Alzheimer patients with debilitation and muscle wasting
• Women over 85, particularly with low body weights, may experience more adverse effects
• For patients with intolerable side effects, generally allow a washout period with resolution of side effects prior to switching to another cholinesterase inhibitor
• Cognitive improvement may be linked to substantial (>65%) inhibition of acetylcholinesterase
• Rivastigmine may be more selective for the form of acetylcholinesterase in hippocampus (G1)

✶ More potent inhibitor of the G1 form of acetylcholinesterase enzyme, found in high concentrations in Alzheimer patient’s brains, than the G4 form of the enzyme
• Butyrylcholinesterase action in the brain may not be relevant in individuals without Alzheimer disease or in early Alzheimer disease; in the later stages of the disease, enzyme actively increases as gliosis occurs
• Rivastigmine’s effects on butyrylcholinesterase may be more relevant in later stages of Alzheimer disease, when gliosis is occurring

✶ May be more useful for later stages or for more rapidly progressive forms of Alzheimer disease, when gliosis increases butyrylcholinesterase
• Butyrylcholinesterase actively could interfere with amyloid plaque formation, which contains this enzyme

• Some Alzheimer patients who fail to respond to another cholinesterase inhibitor may respond when switched to rivastigmine
• Some Alzheimer patients who fail to respond to rivastigmine may respond to another cholinesterase inhibitor
• To prevent potential clinical deterioration, generally switch from long-term treatment with one cholinesterase inhibitor to another without a washout period

✶ May slow the progression of mild cognitive impairment to Alzheimer disease
✶ May be useful for dementia with Lewy bodies (DLB, constituted by early loss of attentiveness and visual perception with possible hallucinations, Parkinson-like movement problems, fluctuating cognition such as daytime drowsiness and lethargy, staring into space for long periods, episodes of disorganized speech)
• May decrease delusion, apathy, agitation, and hallucinations in dementia with Lewy bodies

✶ May be useful for vascular dementia (e.g., acute onset with slow stepwise progression that has plateaus, often with gait abnormalities, focal signs, imbalance, and urinary incontinence)
• May be helpful for dementia in Down’s syndrome
• Suggestions of utility in some cases of treatment-resistant bipolar disorder
• Theoretically, may be useful for ADHD, but not yet proven
• Theoretically, could be useful in any memory condition characterized by cholinergic deficiency (e.g., some cases of brain injury, cancer chemotherapy-induced cognitive changes, etc.)

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