

# drug information perspectives

Volume 28 (1) 2008

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**DEMENTIA THERAPY**

	<b>Donepezil</b>	<b>Galantamine</b>	<b>Memantine</b>	<b>Rivastigmine</b>
<b>Trade Name</b>	Aricept	Reminyl	Ebixa	Exelon
<b>Chemical class</b>	Piperidine alkaloid	Phenanthrene	Amino-adamantane	Carbamate
<b>Mechanism</b>	AcetylChEI* and acts on nicotinic receptors	AcetylChEI	NMDA antagonist	AcetylChEI + butyrylChEI
<b>Indication</b>	Mild-moderate Alzheimer's disease	Mild-moderate Alzheimer's disease	Moderate-severe Alzheimer's disease	Mild-moderate Alzheimer's disease
<b>Food</b>	No effect	No effect	No effect	Increased AUC
<b>Metabolism</b>	CYP2D6,3A4	CYP2D6,3A4	Minimal	Cholinesterases
<b>Half-life</b>	70 hours	10 hours	60-80 hours	1.5 hours but effect lasts 12 hours

\* ChEI = cholinesterase inhibitor

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## CLASSIFICATION

**Donepezil:** Acetylcholinesterase inhibitor; cholinergic

**Galantamine:** Acetylcholinesterase inhibitor; cholinergic

**Memantine:** NMDA receptor antagonist

**Rivastigmine:** Acetylcholinesterase inhibitor; cholinergic

## ACTION

### **Donepezil, galantamine, rivastigmine:**

- Acetylcholinesterase inhibitors increase the level of acetylcholine in neuronal synaptic clefts in the brain.
- Galantamine also increases the effect of acetylcholine at nicotinic acetylcholine receptors in vitro; clinical relevance unproven.
- Rivastigmine also inhibits butyrylcholinesterase; clinical relevance unknown.

**Memantine:** Blocks one of the glutamate receptor types, the NMDA (N-methyl-D-aspartate) receptor, reducing neuronal damage caused by excessive glutamate.

## PHARMACOKINETICS

**Donepezil:** Half-life 70 hours; food does not affect absorption; metabolized by CYP2D6 and 3A4; eliminated in urine; CYP2D6 polymorphism may alter clearance.

**Galantamine:** Half-life 7-10 hours; food has no effect on absorption; metabolized by CYP2D6 and 3A4; 95% eliminated in urine; CYP2D6 polymorphism may alter clearance.

**Memantine:** Half-life 60-80 hours; food has no effect on absorption; 10-25% metabolized but P450 involvement is undefined; eliminated mainly in urine.

**Rivastigmine:** Half-life 1.5 hours; administration with food increases absorption; metabolized by cholinesterases; no P450 metabolism; eliminated in urine; smokers may have increased clearance.

## USES AND EFFICACY

**Uses:** The symptomatic treatment of **Alzheimer's disease:**

- **Mild-moderate Alzheimer's disease:** Donepezil, galantamine, and rivastigmine.
- **Moderate Alzheimer's disease:** Donepezil, galantamine, rivastigmine, memantine, memantine+cholinesterase inhibitor.
- **Severe Alzheimer's disease:** Donepezil (approved in the US), memantine, memantine+cholinesterase inhibitor.

### **Clinical course:**

- Benefit on cognitive function peaks at 3-6 months, then declines gradually. If cholinesterase inhibitor therapy is discontinued, some patients may decline severely.

### **Place in therapy:**

- Dementia is a syndrome consisting of cognitive and functional decline, sometimes accompanied by behavioural and personality change.
- Currently approved cholinesterase inhibitors and an NMDA antagonist offer only symptomatic treatment. There is no proven effect on the underlying progressive disease.
- Study design has been problematic. The therapeutic benefit of cholinesterase inhibitors may have been exaggerated by the use of relatively healthy patients, excluding frail patients with significant comorbid conditions. Real world benefit may also be less than that indicated by Observed Case analysis results: the discontinuation rate due to adverse effects was higher in the cholinesterase inhibitor treatment groups, thus those who completed the studies and were included in the final Observed Case analyses were those who could tolerate the drug. Use of Last-Observation-Carried-Forward-Intention-to-Treat analysis is also problematic in a progressive disease with a high discontinuation rate, especially when withdrawals were mostly in the treatment group as they are for cholinesterase inhibitors, since this will also exaggerate the drug treatment effect. Blinding may have been difficult to maintain given the typical cholinergic side effects seen with cholinesterase inhibitors. Use of the sensitive ADAS-cog to measure cognitive change skews the results towards finding a measurable positive benefit that may not be clinically relevant.

Importantly, it is likely that some of the study patients did not have pure Alzheimer's disease, since the clinical diagnosis of Alzheimer's disease is not always supported by autopsy results, and the patients may have had mixed dementia, commonly mixed vascular dementia with Alzheimer's disease, or a variety of other dementias. Thus, monitoring the response of individual patients is important.

- Personalize therapy based on the goals and dementia stage of the patient.

- **Unknowns:** Which patients will respond is not predictable; ApoE genotype does not predict response. There is no proof of benefits and improved quality of life for the patient, with most assessment tools focused on the observations of caregivers. A publicly-funded study found that cholinesterase inhibitors did not delay institutionalization, a step that is influenced by many factors. This study has been criticized since, among other study limitations, the small number of patients in the study after one year may have made it difficult to detect a statistical treatment difference. There are no data on whether or not life is prolonged. There are ethical concerns. Treatment of severe dementia raises concerns of possibly prolonging suffering, or returning the patient to a less comfortable earlier stage of dementia. Improvement in the quality of life of the patient is expected; if clinical improvement is not seen, the drug should be discontinued.

**Mild-to-moderate Alzheimer's disease:** Donepezil, galantamine, and rivastigmine may temporarily improve or stabilize the symptoms of cognitive deterioration. After 6-12 months, the symptoms of deterioration will noticeably progress at the same rate as without treatment. When treatment is discontinued, patients decline to the same cognitive level as if they had never been treated. The response is variable, with a clinically meaningful improvement (at least a 4 point improvement on ADAS-cog) in only 10-30% more patients than if given a placebo, and temporary stabilization of disease without any noticeable improvement the only response in about one-third of patients. The average response is modest, only a 2-point average improvement over baseline on ADAS-cog (total range 70 points). Activities of daily living rarely improve but may decline more slowly, and behavioural symptoms may improve but this is less well documented. Some experts have questioned the clinical relevance of the small average degree of benefit.

**Moderate Alzheimer's:** A cholinesterase inhibitor, memantine or the combination can be used.

**Severe Alzheimer's disease:** Donepezil is approved in the US for severe Alzheimer's disease; other cholinesterase inhibitors may also be effective. However, when patients reach the severe stage of dementia it is not the cognitive decline, which is the main focus of benefit of cholinesterase inhibitors, but rather the behavioural and neuropsychiatric problems that predominate. The clinical significance of cholinesterase effects in severe disease has been questioned. Patients may already be stabilized on a cholinesterase inhibitor, and adding memantine can add further small benefit. The benefit of switching to memantine monotherapy as the disease progresses is unknown.

#### **Comparisons:**

- Among the cholinesterase inhibitors, no significant differences in efficacy or toxicity have been proven, although direct comparisons are few and suffer from varied patient populations and study designs.
- Some patients who do not respond to or do not tolerate one cholinesterase inhibitor may tolerate or respond to another one. Some patients who do not respond to or tolerate memantine may benefit from a cholinesterase inhibitor.
- **Donepezil** has the advantages of the longest clinical experience, convenient dosing once daily with or without food, simple dose titration, the existence of a dosage form that rapidly dissolves when placed on the tongue, possibly better GI tolerance, and approval in other jurisdictions for treatment of severe Alzheimer's disease, which may enhance continuity of care.
- **Galantamine** has the advantages of a convenient dosage regimen using extended release capsules once daily without regard for meals, and a shorter duration of action than donepezil allowing rapid resolution of side effects.
- **Rivastigmine** has the advantages of a lack of interactions involving P450 enzymes, the availability of an oral solution and a transdermal patch, a shorter duration of action than donepezil allowing rapid resolution of side effects, multiple dosage strengths allowing individualized dosing, and approval in other jurisdictions for the treatment of mild to moderate dementia in Parkinson's disease.
- **Memantine** has the advantages of ease of administration without regard for meals; proven benefit in severe Alzheimer's disease; and due to its different mode of action has a low potential to cause nausea and vomiting.

#### **Investigational/Unapproved Uses:**

- **Lewy body dementia:** Some evidence for benefit with cholinesterase inhibitors. These patients may have a greater cholinergic deficit than those with Alzheimer's disease. A few patients have had improvement or stabilization with memantine. More data are needed.

- **Mild cognitive impairment:** Galantamine was shown to be ineffective in two controlled studies. In these studies the risk of death was increased, mainly from cerebrovascular or cardiovascular causes.
- **Parkinsons Disease with dementia:** These patients may have a greater cholinergic deficit than patients with Alzheimer's disease. Some cholinesterase inhibitors have improved hallucinations, memory, cognition and behaviour, and rivastigmine is approved in the US for this indication, but improvements in executive dysfunction are less clear. Parkinsonism may worsen.
- **Schizophrenia:** Abnormal cholinergic transmission at nicotinic receptors may exist. In a number of cases and two small controlled studies, benefits were seen in cognition, memory, attention and negative symptoms. Modest improvements but results are mixed and the data are inconclusive. Some patients with catatonic schizophrenia have benefited from memantine.
- **Supranuclear palsy:** Movement disorders worsen with donepezil.
- **Traumatic brain injury:** An open trial of galantamine and other cholinesterase inhibitors found that 40-60% of patients rapidly improved subjectively in vigilance, concentration and general function.
- **Vascular dementia:** Autopsies show that many elderly people have both Alzheimer's disease and vascular dementia. Patients with mixed Alzheimer's disease and cardiovascular disease show improvement with both memantine and cholinesterase inhibitors. Theoretically beneficial due to cholinergic deficits observed in vascular dementia.

## CONTRAINDICATIONS AND PRECAUTIONS

### Contraindications:

- **Hypersensitivity**
- **Lactose intolerance and related disorders** (galantamine tablets contain lactose)
- **Amantadine, ketamine, dextromethorphan** (similar structure to memantine)
- **Cardiac conduction abnormalities** including sick sinus syndrome and history of unexplained syncope (vagotonic effect of cholinesterase inhibitors can cause heart block)
- **Severe hepatic impairment** (galantamine, rivastigmine)
- **Severe renal impairment** (galantamine, memantine)
- **Children** (no data; not indicated)
- **Mild cognitive impairment** (increased risk of death with galantamine)

### Precautions:

- **Cholinesterase inhibitors:** Caution in conditions that can worsen due to cholinergic effects: coronary heart disease, heart failure, GI ulcers and bleeds, urinary bladder outflow obstruction, epilepsy or seizure history, asthma and COPD (risk of heart block, gastric acid secretion, urinary obstruction, seizures, bronchoconstriction). Atropine is antidotal.
- **Cholinesterase inhibitors:** Caution in patients with impaired renal or liver function (risk of increased drug levels)
- **Memantine:** Caution in patients with alkaline urine (increased drug levels); cardiovascular disease (possible cardiac toxicity); renal impairment (reduce dose).
- **Reminyl:** Medication error hazard: Prescriptions for Reminyl and sound-alike Amaryl (glimepiride) have been incorrectly dispensed, leading to fatal hypoglycemia.
- **Slow dose titration** (follow guidelines to avoid side effects).
- **Avoid sudden withdrawal** (drug withdrawal syndrome has been reported; sudden decline may occur).
- **Report** unexpected or serious reactions to the Canada Vigilance Program (Health Canada's postmarketing surveillance program).

## PREGNANCY AND LACTATION

- **Cholinesterase inhibitors:** Galantamine: possible teratogenicity in rats. Rivastigmine: no data. Assess risk:benefit. Not recommended during lactation due to potential cholinergic effects.
- **Memantine:** No data.

## SIDE EFFECTS

- **Cholinesterase inhibitors:** Common effects are usually not serious and include cholinergic toxicities of nausea, vomiting, diarrhea, anorexia, weight loss, abdominal pain and tremor, as well as dizziness and headache. The cholinergic effects are dose-related, and occur most frequently during the initial dose titration phase, by the end of which most patients develop tolerance. As such, a slow dose titration will reduce their frequency, and restarting at a low dose is essential if a patient loses tolerance by missing several days of therapy. Despite slow dose initiation,

approximately 20% of patients cannot tolerate these drugs. Serious adverse reactions are rare: bradycardia, heart block, arrhythmias requiring a pacemaker, seizures, syncope, falls, fractures, severe weight loss, severe vomiting leading to esophageal rupture, or dehydration rarely leading to renal failure. Withdrawal syndrome can occur (agitation, sleep disturbance, mood changes).

- Some evidence suggests that donepezil may cause less GI toxicity than rivastigmine or galantamine.
- **Memantine**: Common side effects include dizziness, constipation, confusion and increased blood pressure. Less commonly, bradycardia, hallucinations, fatigue, agitation, or seizures may occur.

## INTERACTIONS

### **Acetylcholinesterase inhibitors:**

- **Increased cholinergic effect**: Cholinergic drugs, inhibitors of CYP2D6 and 3A4, combined cholinesterase inhibitors; beta blockers, calcium channel blockers, digoxin (additive bradycardia); NSAIDs (increased gastric irritation).
- **Decreased cholinergic effect**: Anticholinergic drugs.
- **Increased effect of interacting drug**: Succinylcholine (depolarizing neuromuscular blockade).

### **Memantine:**

- **Increased memantine toxicity**: Drugs that alkalinize the urine: carbonic anhydrase inhibitors, sodium bicarbonate; drugs using the same renal elimination system: cimetidine, hydrochlorothiazide, nicotine, quinidine, ranitidine, triamterene; drugs with additive effects on NMDA receptors: amantadine, ketamine, dextromethorphan.
- **Increased effect of interacting drug**: Drugs metabolized by CYP2B6 (memantine inhibits their metabolism); levodopa.

## DOSAGE

### **Guidelines**

- **Starting therapy**: Perform baseline MMSE and ADL; start drug at low dose and slowly increase dose at the intervals specified for that drug. If side effects occur, discontinue for several doses then restart at a lower dose or the same dose level. Adjust dose to patient tolerance. Evaluate benefit after 3-6 months.
- **Identifying responders**: There is no agreement on how to identify responders. Individualize depending on the goals for that patient. Untreated patients deteriorate approximately 2 points on MMSE over one year, but it is highly variable. Some experts define a response as an increase of at least 2 points on MMSE. Generally, if MMSE is stable or improved, continue initial therapy for another 3-6 months then re-evaluate. If deteriorating, consider another cholinesterase inhibitor or memantine. Given the small drug effect and the insensitivity of the MMSE for detecting small changes, it may be difficult for a clinician to detect a response.
- **Administration** with food or antiemetic drugs and giving adequate fluid intake may reduce GI side effects from cholinesterase inhibitors.
- **Adequate trial**: 3-6 months.
- **Discontinuing therapy**: Consider if therapy is helping the patient's specific symptoms, in which case treatment may continue for years. Discontinue if unacceptable adverse effects develop or there is clear progression of disease. If unsure, consider a drug holiday for 4-6 weeks; if there is abrupt worsening, the drug may be reintroduced, keeping in mind that the disease is progressive. It may be wise to taper the dose to avoid a withdrawal syndrome.
- **Switching cholinergic drugs**: Some patients who do not tolerate or respond to one drug may benefit from another one. There is no consensus on the need for a washout period between drugs; it depends on the reason for switching. If switching because of adverse effects, then a washout period of at least 14 days or until all toxicity has resolved is recommended in order to avoid cholinergic toxicity. A decline in function may occur during the transition. If switching because of lack of response, some clinicians do not use a washout period since the dose of the new drug will be slowly titrated up from an initial low dose. Individualize taking into consideration the dose and pharmacokinetics of the first drug, as well as the condition of the patient. Start the new drug at the lowest dose, slowly increase the dose, and monitor carefully. If cholinergic toxicity appears, discontinue the new drug until symptoms resolve. If the patient's dementia worsens, it may be necessary to restart the first drug.
- **Switching from cholinesterase inhibitors to memantine as dementia worsens**: To reduce the risk of withdrawal effects from stopping the cholinesterase inhibitor, some experts suggest overlapping therapy for one month.

## MEMANTINE

**TRADE NAME:** Ebixa

### CLASSIFICATION

- NMDA receptor antagonist
- Dementia therapy
- Aminoadamantane

### ACTION

- NMDA (N-methyl-D-aspartate) receptor blocker.
- Use in Alzheimer's and other neurodegenerative diseases is based on the "glutamate hypothesis": excessive stimulation by glutamate, the major excitatory amino acid in the brain, causes neuronal damage and death. Memantine blocks one of the glutamate receptor types, the NMDA receptor, reducing neuronal damage. It is low-affinity (theoretically this reduces toxicity), open-channel and uncompetitive (the receptor already has to be activated, thus it only works if pathological excess glutamate stimulation occurs, without harming essential glutamate function).
- NMDA receptors also exist in the heart, lungs and pancreatic beta cells.
- Other NMDA blockers include amantadine, ketamine, phencyclidine and nitroglycerin.
- Other actions may include: 5HT<sub>3</sub>-type serotonin receptors and NMDA receptors are blocked with equal potency; may increase dopamine release.

### PHARMACOKINETICS

#### *Half-life:*

- 60-80 hours.

#### *Absorption:*

- 100% oral absorption with peak levels after about 5 hours. Food does not alter absorption.

#### *Distribution:*

- Protein binding 45%.
- Accumulates in temporal lobe, hypothalamus, pons.

#### *Metabolism:*

- 10-25% metabolized to products with little activity. P450 enzymes are not highly involved.

#### *Elimination:*

- Mainly eliminated in urine as unchanged drug. Active renal tubular secretion and reabsorption occur. Renal elimination severely reduced if urine is alkaline because the drug is a weak base (80% reduction at pH 8).

#### *Special populations:*

- *Elderly:* No change.
- *Hepatic impairment:* No data.
- *Renal impairment:* Mild impairment: Exposure increases 14%. Moderate impairment: Exposure increases 39-60%. Severe impairment: Increased AUC 115%, increased half-life 95%, decreased clearance.

### USES AND EFFICACY

*Uses:* The symptomatic treatment of **moderate to severe Alzheimer's disease**, either as monotherapy or in combination with cholinesterase inhibitors. As monotherapy, there is slightly but statistically significantly less deterioration in global function, activities of daily living, and cognition, as measured by CIBIC-Plus, ACDCS-ADLsev and SIB over 6 months. Behaviour may improve but evidence is less strong (2.7 point improvement on 144 point NPI). Adding memantine to existing cholinesterase inhibitor treatment may improve cognition in 12% more patients than with placebo, as well as modestly reducing the symptoms of deterioration in activities of daily living, global function and behaviour.

#### *Clinical course*

- Improvement in cognition and ADL may be detectable within 2-12 weeks.

#### *Major clinical trials*

*Moderate to severe Alzheimer's disease (2003):* A randomized, placebo-controlled trial evaluated memantine 20mg/day in 252 community-dwelling patients with average MMSE 8 at baseline. Exclusions included any patients

with significant comorbidities, vascular dementia or major depression. After 6 months, the patients given memantine had deteriorated statistically significantly less in global function (by 0.3 points on 7 point CIBIC-Plus), activities of daily living (3.4 points on 54 point ADCS-ADLsev scale), and cognition (5.7 points on 100 point SIB) compared to placebo. Behaviour as indicated by NPI was not different. More patients taking memantine were able to complete the study (90% versus 83%). An open label extension for a further 6 months did not find any sign of tolerance to memantine. More patients discontinued memantine than placebo, mainly due to side effects. Limitations: Many common types of patients were excluded. More patients in the placebo group discontinued therapy initially, thus the benefit may be underestimated.

**MEM-MD-01 Moderate to severe Alzheimer's disease (unpublished) 2005:** A randomized, double-blind, placebo controlled study of 350 patients with MMSE 5-14 compared memantine with placebo for 24 weeks. Discontinuation rates were 25% in both groups. Results on SIB, ADCS-ADLsev, CIBIC-Plus and NPI did not find a significant difference between memantine and placebo. Adverse event rate was similar.

**Add-on therapy with cholinesterase inhibitors (2004):** A randomized, double-blind, placebo controlled trial in 404 patients with moderate to severe probable Alzheimer's disease (mean MMSE 10) studied the effect of adding memantine to patients who were already stabilized on donepezil. After 6 months, more patients had withdrawn from the study in the placebo group (25%) than in the memantine group (15%). Patients given memantine improved in cognitive function (3.4 points on 100 point SIB), and deteriorated statistically significantly less in global function (by 0.3 points on 7 point CIBIC-Plus), activities of daily living (1.6 points on 54 point ADCS-ADLsev scale), and behaviour (3.4 points on 144 point NPI) compared to placebo. Fifty-five percent of patients were unchanged or improved when taking memantine compared with 45% of those taking placebo (NNT=10).

#### **Comparisons**

- **Versus donepezil:** Both memantine and donepezil show modest benefit in severe Alzheimer's disease; no direct comparisons have been made and studies have used patients with different disease severity.
- **Versus galantamine, rivastigmine:** No data.

#### **Advantages:**

- May increase autonomy.
- May reduce agitation.

#### **Disadvantages:**

- No data on patient quality of life.

#### **Place in therapy:**

- Modestly improves symptoms in patients with moderate or severe Alzheimer's disease.
- Monotherapy may be more effective than combining it with a cholinesterase inhibitor.
- May reduce agitation.
- Patients have been better at group activities and basic actions such as moving, washing, and toileting than if not given the drug.
- Despite continued therapy, the disease progresses.
- The response rate for adding on memantine, defining response as no change or improvement, is only about 10% better than placebo plus a cholinesterase inhibitor (NNT=10), and very few patients display a striking improvement.
- Benefits are highly variable, with a subgroup attaining a clinically meaningful response. Responders should be identified and their treatment continued. Nonresponders should be identified and the drug discontinued.
- It helps only the symptoms and does not alter the course of the disease. Although animal models have documented neuroprotection, there is no evidence for this in humans.
- No proven ability to delay institutionalization.

#### **Investigational/Unapproved Uses:**

- Some study details may be found at [www.forestclinicaltrials.com](http://www.forestclinicaltrials.com) and [www.clinicaltrials.gov](http://www.clinicaltrials.gov).
- **Acquired pendular nystagmus in multiple sclerosis:** Case reports of complete recovery have been published.
- **Glaucoma:** Based on the unproven theory that glutamate excitotoxicity may be involved in the development of glaucoma, which is supported by neuroprotective effects of memantine in animal models of glaucoma, a phase III trial is currently in process.

- **Lewy body dementia:** A few cases reported improvement or stabilization of cognition, ADL, or parkinsonism, but some patients have developed increased hallucinations or delusions.
- **Mild to moderate Alzheimer's disease:** A small benefit on cognition has been reported.
- **Obsessive-compulsive disorder:** Mixed results.
- **Pain:** Tested in neuropathic pain based on the efficacy of another NMDA antagonist, ketamine, in this condition. Studies have not found any benefit in painful diabetic neuropathy, phantom limb pain, or nerve pain after surgery.
- **Parkinson's Disease:** Was developed in the 1970's in Europe for Parkinson's disease; may affect dopamine. May interact with levodopa therapy.
- **Schizophrenia:** Patients with catatonic schizophrenia have benefited, as suggested by positive dechallenges and rechallenges.
- **Vascular dementia:** In a randomized, placebo-controlled study in outpatients with mild to moderate vascular dementia, patients given memantine had a small benefit in cognition as indicated by a 1.8 point difference in the change in ADAS-cog compared with placebo, but there was no significant effect on global function detected by the clinician and caregivers. In contrast, in a study of moderately severe to severe Alzheimer's or vascular dementia there were improvements in global function, independence and behaviour, irrespective of diagnosis.

## CONTRAINDICATIONS AND PRECAUTIONS

### Contraindications:

- **Hypersensitivity**
- **Amantadine** (similar chemical structure and possible additive toxicity)
- **Ketamine** (similar chemical structure and possible additive toxicity)
- **Dextromethorphan** (similar chemical structure and possible additive toxicity)
- **Severe renal impairment** (no data; most elimination is renal)
- **Children** (no data; not indicated)

### Precautions:

- **Seizure disorders, epilepsy** (no safety data)
- **Alkaline urine** (increased urine pH), due to drugs or conditions such as a switch to vegetarianism, renal tubular acidosis, certain urinary tract infections (decreased clearance and increased drug levels)
- **Cardiovascular diseases** (possible hypertension, bradycardia, heart failure or chest pain)
- **Monitor vision** (risk of histopathological changes in cornea or lens)
- **Moderate renal impairment** (reduce dose due to decreased elimination)
- **Slow dose titration** (follow guidelines to avoid side effects).
- **Report** unexpected or serious reactions to the Canada Vigilance Program (Health Canada's postmarketing surveillance program).

## PREGNANCY AND LACTATION

- No known teratogenicity in animals. No data on effects during pregnancy in humans; assess risk:benefit.
- No data on excretion into breast milk or effects on nursing infants. Not recommended during lactation.

## SIDE EFFECTS

- Well tolerated. The most common effect is dizziness.

**Cardiovascular:** Hypertension (7.9% versus placebo 2.3%), bradycardia, heart failure or chest pain.

**CNS:** Dizziness (11% versus placebo 8%); headache (5.6% versus placebo 3.6%); confusion (7.9% versus placebo 2.0%; usually mild, delayed and reversible, may respond to dosage reduction); hallucinations (5% versus placebo 2%); fatigue (2.3% versus placebo 0.7%); pain (2.4% versus placebo 1%); anxiety (2.6% versus 0.8%); akathisia and increased motor activity, excitement, agitation, insomnia; seizures (cases). Psychosis at 10-30mg/day (above recommended dose) in patients with Parkinson's disease.

**Gastrointestinal:** Constipation (10% versus placebo 4%); anorexia (2.2% versus placebo 1.2%).

**Other:** Histopathological changes in the cornea or lens in animals and rarely in humans; abnormal gait (3% versus placebo 1%); hyperglycemia (frequent); falls (case reports); spontaneous bruising or purpura.



## INTERACTIONS

Memantine inhibits CYP2B6.

DRUG	EFFECT	MECHANISM	IMPORTANCE
Amantadine	Possible psychosis	Additive effect on NMDA receptors	Contraindicated
Carbonic anhydrase inhibitors (acetazolamide)	Increased memantine levels	Decreased memantine clearance with alkaline urine	Caution
Dextromethorphan	Possible psychosis	Additive effect on NMDA receptors	Contraindicated
Drugs metabolized by CYP2B6*	Increased drug level	Decreased metabolism (CYP2B6)	Caution (theoretical)
Drugs with similar renal elimination**	Increased memantine effects	Decreased renal elimination	Caution (theoretical)
Ketamine	Possible psychosis	Additive effect on NMDA receptors	Contraindicated
Levodopa	Increased levodopa effect	Memantine releases dopamine	Caution
Sodium bicarbonate	Increased memantine levels	Decreased memantine clearance with alkaline urine	Caution

\*Drugs metabolized by CYP2B6 include: Bupropion, cyclophosphamide, diazepam, mephenytoin, midazolam, tamoxifen.

\*\*Drugs with similar renal elimination to memantine, using the renal cationic transport system, include: Cimetidine, hydrochlorothiazide, nicotine, quinidine, ranitidine, triamterene.

### ***Interactions lacking***

A lack of pharmacokinetic interaction has been documented with

- Glyburide
- Metformin

## **DOSAGE**

### ***Guidelines***

- Adjust dose to patient tolerance.

### **Adults:**

#### **Alzheimer's disease:**

- Oral: Initially 5mg/day. After at least one week, if tolerated, increase to 10mg/day (5mg twice daily). After at least one further week, if tolerated, increase to 15mg/day in two divided doses. After at least one further week, if tolerated, increase to 20mg/day (10mg twice daily).

- Maximum 20mg per day.

#### **Acquired pendular nystagmus** in multiple sclerosis (investigational):

- Oral: Initially 5 mg/day. Maximum 20mg/day (10mg twice daily).

### **Elderly:**

- No dosage change required unless renal function is impaired.

### **Hepatic impairment:**

- No dosage change expected since little metabolism occurs.

### **Renal impairment:**

- Mild impairment: No dosage change.

- Moderate impairment (ClCr 40-60mL/minute): Reduce dose to 10mg per day.

- Contraindicated in severe impairment.

## **NURSING IMPLICATIONS**

This medication can be taken with or without food.

The most common side effects are dizziness, confusion and constipation. Monitor for any changes in the patient's condition.

Therapeutic benefit when used in Alzheimer's disease may include an improvement in activities of daily living, such as improved independence, attentiveness, memory and ability to converse, and improved behaviour.

See PATIENT INSTRUCTIONS.

## **PATIENT INSTRUCTIONS**

Memantine (meh-MAN-teen) is a drug used to treat the symptoms of Alzheimer's disease.

Before taking this medication, be sure that the physician is aware if you have: kidney disease, allergies, seizure disorder or epilepsy, urinary tract infection, recent switch to vegetarianism (alkaline urine can increase levels of the drug), heart disease, vascular disease, high blood pressure, heart failure, constipation, or diabetes, or if you take amantadine, ketamine or dextromethorphan.

This medication should be taken exactly as prescribed by the physician. It is taken every day for best results. Do not stop taking it suddenly; consult your physician if you wish to stop taking it.

This medication can be taken with food or on an empty stomach.

If a dose is missed, take it if it has only been a few hours. Otherwise, skip that dose and take the next one at the usual time. Don't take a double dose to make up for a missed one.

This medication can interact with other medications. Inform your physician and pharmacist of all other medications that you are taking.

Side effects are usually mild. Tell your physician if you develop any unexpected or serious effects after starting this medication, especially dizziness, or vision problems.

If you have experienced an unexpected or serious reaction to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number.

Store this drug in its original container, away from heat, light and moisture, and out of the reach of children.

**PRESENTATION**

Tablet: 10 mg.

References are available on request.