

NEW DRUG UPDATE

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Namenda® (memantine)

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Introduction

Namenda® [memantine hydrochloride (me-MAN-teen)] is an orally active, noncompetitive NMDA receptor antagonist. It represents the first member of a new class of medications showing clinical benefit and good tolerability in Alzheimer Disease (AD). Memantine hydrochloride received FDA approval in October 2003 for the treatment of moderate to severe dementia of the Alzheimer's type.

Therapeutic Recommendation

In a study comparing memantine plus donepezil (a cholinesterase inhibitor) to donepezil alone, a 55% response rate was seen in the memantine group vs. a 45% response rate in the placebo group based on clinician and caregiver input. Another study indicated that caregivers spent less time with patients receiving memantine (difference between memantine vs. placebo, 45 hours per month). In patients with moderate-to-severe AD receiving stable doses of donepezil, memantine resulted in significantly better outcomes than placebo on measures of cognition, activities of daily living, and

behavior and was well tolerated. It is the only drug indicated to treat moderate-to-severe AD. Efficacy of memantine is still unclear in patients with mild AD. Monotherapy with cholinesterase inhibitors remains the treatment of choice in patients with mild AD. Although memantine has not shown clinical benefit in patients with mild AD, future studies may indicate its use in patients intolerant or resistant to treatment with cholinesterase inhibitors. Although approved for monotherapy, memantine appears to work best when used in conjunction with cholinesterase inhibitors in moderate-to-severe AD. Memantine is not a cure for AD, and its true clinical benefit and cost must be taken into account when prescribing this medication. When monitoring memantine therapy, clinicians and caregivers should evaluate the functional status and behaviors of the patient, as well as adverse effects (most commonly headache and confusion).

Dosing and Administration

Memantine hydrochloride is available as 5 mg and 10 mg tablets. The recommended starting dose of memantine hydrochloride is 5 mg once daily. The recommended target dose is 20 mg/day. The dose should be increased in 5 mg increments to 10mg/day (5 mg twice a day), 15 mg/day (5 mg and 10

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mg as separate doses), and 20 mg/day (10 mg twice a day). The minimum recommended interval between dose increases is one week.

Cost Comparison

Medication/Dose	Cost [^]		
	<u>KMart</u>	Kroger	<u>Rite Aid</u>
Namenda® (memantine HCL) 5 mg BID	144.97	169.69	150.99
Namenda® (memantine HCL) 10 mg BID	144.97	169.69	150.99
Namenda® (memantine HCL) Titration pack 49 tabs 200 mg	118.97	132.69	122.99
Aricept® (donepezil HCL) 5 mg, 10 mg QD	150.39	179.69	168.99

[^]Cost to patient for a 30-day supply of the regimens provided; no generics available

Contraindications

Memantine hydrochloride is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

Use caution with seizure disorders, hepatic and mild-to-moderate renal impairment. Clearance is significantly reduced by alkaline urine. Use caution with medications, dietary changes, and conditions that may alter urine pH.

Special Populations

Hepatic Impairment: Memantine hydrochloride un-

dergoes partial hepatic metabolism, but the major fraction of a dose (57-82%) is excreted unchanged in urine. The pharmacokinetics of memantine hydrochloride in patients with hepatic impairment has not been investigated, but would be expected to be only modestly affected.

Renal Impairment: There are inadequate data available in patients with mild, moderate, and severe renal impairment but it is likely that patients with moderate renal impairment will have higher exposure than normal subjects. Dose reduction in these patients should be considered. Memantine hydrochloride in patients with severe renal impairment should be used cautiously, perhaps with a longer titration schedule.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: There was no evidence of carcinogenicity, genotoxicity, or impairment of fertility or reproductive performance in mice and rats.

Pregnancy: Memantine hydrochloride is categorized as pregnancy category B. There are no adequate and well-controlled studies of memantine hydrochloride in pregnant women and it is not indicated for use in this population.

Nursing Mothers: It is not known whether memantine hydrochloride is excreted in human, breast milk and it is not indicated for use in nursing mothers.

Pediatric Use: There are no adequate and well-controlled trials documenting the safety and efficacy of memantine hydrochloride in any illness occurring in children.

Drug Interactions

Increased effect/toxicity-Clearance of memantine hydrochloride is decreased 80% at urinary pH 8;use caution with medications (carbonic anhydrase inhibitors, sodium bicarbonate) which may increase urinary pH.

The combined use of memantine hydrochloride with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

No CYP450 drug interactions occur with memantine hydrochloride.

Coadministration of memantine hydrochloride with the AchE inhibitor donepezil HCL did not affect the pharmacokinetics of either compound. In a 24-



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week controlled clinical study in patients with moderate to severe AD, the adverse event profile observed with a combination of memantine hydrochloride and donepezil was similar to that of donepezil alone.

Because memantine hydrochloride is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of memantine hydrochloride and HCTZ/TA did not affect the bioavailability of either memantine hydrochloride or TA, and the bioavailability of HCTZ decreased by 20%.

Common Adverse Effects

The most common adverse effects reported in clinical trials with memantine hydrochloride plus donepezil vs. donepezil alone were confusion (7.9% vs. 2.0%) and headache (6.4% vs. 2.5%). Other reported adverse effects included: fall (7.4% vs. 7.0%), influenza-like symptoms (7.4% vs. 6.5%), constipation (3.0% vs. 1.5%), and urinary incontinence (5.4% vs. 3.0%). Incidence of GI related adverse events were seen more frequently in the donepezil alone group: diarrhea (4.5% vs. 8.5%), fecal incontinence (2.0% vs. 5.0%), and nausea (0.5% vs. 3.5%). Overall, adverse events were rated as mild or moderate in severity. Memantine hydrochloride is better-tolerated, than cholinesterase inhibitors.

Pharmacology

Mechanism of Action: Glutamate is an amino acid which may contribute to the pathogenesis and symptomatology of AD by over-stimulating the N-methyl-D-aspartate (NMDA) receptor. Memantine hydrochloride exerts its therapeutic effect through its action as a low to moderate affinity NMDA antagonist binding preferentially to the NMDA receptor-operated cation channels, blocking the effects of glutamate. Memantine hydrochloride has not been shown to prevent or slow neurodegeneration associated with AD.

Absorption/Distribution: Following oral administration memantine hydrochloride is highly absorbed with peak concentrations reached in about 3-7 hours. Food has no effect on the absorption of memantine hydrochloride. The mean volume of

distribution of memantine hydrochloride is 9-11 L/kg and the plasma protein binding is low (45%).

Metabolism/Excretion: Memantine hydrochloride undergoes little metabolism, with the majority (57-82%) of an administered dose excreted unchanged in urine; the remainder is converted primarily to three polar metabolites: the N-gludantan conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine. These metabolites possess minimal NMDA receptor antagonist activity. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of memantine hydrochloride. Memantine hydrochloride has a terminal elimination half-life of about 60-80 hours. Renal clearance involves active tubular secretion moderated by pH dependent tubular reabsorption.

Patient Information

1. Patients can take the medication with or without food.
2. Caregivers should watch for agitation, confusion, dizziness, hallucinations, inability to hold urine, shortness of breath, swelling of the throat or tongue, skin rash or redness, peeling of the skin and vomiting, and should report these to their physician or pharmacist as soon as these symptoms occur.
3. Patients/caregivers should tell their prescriber or health care professional about all other medications they are taking, including non-prescription medications, nutritional supplements, or herbal products.
4. Patients may get dizzy or feel faint. While patients with mild-moderate AD should not be driving or using machinery, using memantine hydrochloride may impair their mental alertness further.
5. Caregivers should be encouraged to monitor and report any progression of AD symptoms and caregiver burden to their health care provider in addition to adverse effects of the medication.

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Humira® (adalimumab)

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Introduction

Humira® [adalimumab (ay-da-LIM-yoo-mab)], approved December 2002, is a biologic therapy available for rheumatoid arthritis (RA). It binds to and blocks the inflammatory effects of tumor necrosis factor alpha (TNF alpha), which reduces joint tenderness, pain, and inflammation, and can retard or prevent future progression of joint destruction.

Therapeutic Recommendation

Adalimumab is the third TNF-alpha inhibitor approved to reduce the signs and symptoms of RA in adults. It is also approved for patients with moderate to severe RA to slow the progression of joint damage. It is used primarily when patients fail to respond to disease-modifying antirheumatic drugs (DMARDs) or methotrexate. It may be used as monotherapy or in conjunction with methotrexate or other DMARDs.

Clinical studies ranging from 24—52 weeks indicate that adalimumab produces improvement versus placebo in Health Assessment Questionnaire Disability Index and the physical and mental components of the Short Form Health Outcomes Survey (SF-36). Additionally, patients treated for 12 months with adalimumab and methotrexate appear to have less radiographic progression than patients treated with methotrexate alone.

Studies indicate that improvement of RA signs and symptoms may be evident as early as one week after starting therapy with adalimumab and symptom relief has maintained for three years. At this time, studies have not been performed to compare adalimumab to etanercept and infliximab. However, some clinicians con-

sider the relative half-life of each agent when selecting which TNF-alpha inhibitor to use, particularly in patients who may be susceptible to infections (such as those aged > 65 years). Use of an agent with shorter half-life may reduce risk to the patient upon drug discontinuation of the drug, should an infection occur. Etanercept has the shortest half-life (115 hr), followed by infliximab (9 days), and then adalimumab (14 days).

Dosing and Administration

Adalimumab is available as a prefilled glass syringe: 40 mg (0.8 ml) or a glass vial: 40 mg (0.8 ml). The recommended adult dosage of adalimumab is 40 mg subcutaneously every other week, and it may be administered with other DMARDs. Some patients, specifically those not concurrently receiving methotrexate, may require a weekly dosage regimen. Preferred sites of injection include the fronts of the thighs and the abdomen, two inches around the navel. Rotation of the injection sites is imperative when administering adalimumab. Sites of the skin that are red, tender, hard, or bruised should be avoided. It should be stored in the refrigerator and discarded if the solution appears discolored.

Cost Comparison

Medication/Dose	Cost [^]		
	CVS	Kroger	Rite Aid
Humira® (adalimumab) 40mg SQ every other week	1,341.99	1,443.89	1,375.99
Enbrel® (etanercept) 25 mg SQ twice weekly	1,377.98	1,442.78	1,433.99
Remicade® (infliximab) 3-5 mg/kg IV at 0, 2, 6 weeks then every 8 weeks	1,453.98	1,383.22	1,505.98

[^]Costs represent price to patient for an average 30-day supply.

Contraindications

Adalimumab is contraindicated in patients with a known allergy to the medication or any individual component.

Black Box Warning

Adalimumab has a black box warning that cautions against the risk of infections, specifically tuberculosis. Physicians should evaluate patients for a latent tuberculosis infection and treat prior to initiation of adalimumab therapy, where appropriate.

Special Populations

Pregnancy: Pregnancy Category B. Adalimumab should be used cautiously and only when necessary during pregnancy.

Nursing Mothers: At this time, it is unknown if adalimumab is excreted in the breast milk. A decision should be made to either discontinue nursing or to discontinue the medication, considering the mother's perceived benefits.

Pediatric Use: The safety and efficacy of adalimumab has not been established in the pediatric population at this time.

Geriatric Use: Caution should be used when treating the elderly with adalimumab because of their increased incidence of infections and malignancies.

Drug Interactions

Methotrexate - can decrease the clearance of adalimumab by 29-44%. No dosage adjustments are required when given concurrently with adalimumab.

Other Immunosuppressant Drugs (i.e., Corticosteroids) - can increase the possibility of developing serious infections. Monitor patients carefully for signs of infection.

Live Vaccines - may reduce the effectiveness of either or both therapies. Avoid using concomitantly.

Adverse Effects

More common:

Injection site reactions, nausea and stomach upset, headache, rash, and infections, including upper respiratory tract infection and sinusitis.

Less common, but serious:

An increased incidence of lymphoma has been associated with use of all three available TNF-alpha inhibitors. It is unclear to what degree the disease process (RA) or methotrexate use plays in causality, versus use of the TNF-alpha inhibitor.

Demyelinating diseases, such as multiple sclerosis, have been worsened or attributed to use of these agents. A reversible lupus-like syndrome has been reported with use of the TNF-alpha inhibitors. Heart failure exacerbations have also been reported with infliximab and etanercept.

Pharmacology

Mechanism of Action: Adalimumab is a monoclonal antibody that binds to human tumor necrosis factor alpha (TNF-alpha) receptor sites. TNF-alpha, a cytokine involved in inflammatory and immune response, is prevented from interfering with its receptors, thus deterring the intensification of the disease process.

Absorption/Distribution: A 40 mg dosage of adalimumab has a maximum serum concentration (C_{max}) of 4.7 ± 1.6 mcg/mL. The time to reach maximum concentration (T_{max}) for the 40 mg dosage is 131 ± 56 hours. Researchers estimate the average bioavailability to be 64% from three studies that each used a single 40 mg dosage. The volume of distribution is 4.7-6 L.

Metabolism/Excretion: The systemic clearance and half-life of adalimumab are 12 mL/hr and about 14 days (ranged from 10-20 days), respectively. Adalimumab clearance increases in the presence of anti-adalimumab antibodies and decreases in patients greater than 40 years old.

Patient Information

1. Adalimumab is for patients with severe rheumatoid arthritis that have not achieved significant responses from other medications. It works by blocking tumor necrosis factor alpha (TNF-alpha), a substance in your body that, when in excess, can lead to inflammation in certain tissues, such as joints and bones.
2. Do not take adalimumab if you are allergic to it or any of its components (sodium phosphate, citric acid, sodium citrate, mannitol, and polysorbate 80). It comes in a pre-filled syringe, and its needle cover contains dry natural rubber. Inform your physician if you have any allergies to rubber or latex.
3. Before beginning adalimumab, inform your physician if you currently have or have experienced any of the following:
 - any infection (either localized or whole body) or a history of infections- having an infection could increase the risk of side effects
 - tuberculosis or have been in contact with someone that has had tuberculosis- if you develop any symptoms consistent with tuberculosis, (such as a persistent dry cough, fe-

- ver, and weight loss), contact your physician, and he/she will perform a TB skin test
- a history of having a disease that effects your nervous system, such as multiple sclerosis
 - any lack of sensation or tingling
 - a scheduled vaccination or major surgery
4. The most common side effect seen with adalimumab is a mild redness and rash around the injection site. It may swell and itch, but the reaction should go away within a few days. Soaking a towel in cold water and applying it to the area can help relieve some of the symptoms, but if it does not get better, no-

tify your physician. Other common side effects include nausea, headache, and upper respiratory infections.

5. Adalimumab comes in a prefilled syringe and is injected under the skin once every other week, unless otherwise prescribed by your physician. If you forget to take your dose at the scheduled time, take it as soon as you remember and take your next dose at the next scheduled time. Adalimumab can be injected into the front of the thighs or the abdomen and a different site should be chosen for each injection. Remember to store the medication in the refrigerator.

References

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