



Pharmacy

January/February 2004

Update

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Medication Utilization Evaluation: Antiemetic Therapy with Ondansetron and Granisetron

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A medication utilization evaluation (MUE) was conducted by the Pharmacy Department to evaluate the utilization of ondansetron and granisetron over an 8-week period in July and August of 2003. Ondansetron (Zofran®) and granisetron (Kytril®) are both NIH Clinical Center (CC) formulary antiemetic agents of the 5-HT₃ serotonin receptor antagonist class. The 5-HT₃ receptor antagonists are effective antiemetics for the prevention of chemotherapy-induced nausea and vomiting (CINV), prevention of radiation-induced nausea and vomiting (RINV), and prevention and treatment of post-operative nausea and vomiting (PONV). However, this class of agents continues to be a high-cost expenditure for the clinical center. The MUE was conducted as a follow-up to the recently revised NIH CC antiemetic guidelines which were finalized in January of 2003 (see *Pharmacy Update* Jan/Feb 2003). During the MUE period, pharmacists were asked to retain a copy of all orders for either ondansetron or granisetron and complete a MUE questionnaire. The data collected for the MUE focused primarily on the clinical indication and the prescribed dosing regimen.

The results of the MUE revealed the following:

- ❖ Ondansetron was the predominant 5-HT₃ receptor antagonist prescribed (96% of orders) during the MUE period. This finding was consistent with the recommendation of the 2003 NIH CC antiemetic guidelines when ondansetron was selected as the primary formulary antiemetic.
- ❖ Seventy percent of the orders were within the guideline's prescribing indications. The most common indications were acute CINV prophylaxis and delayed CINV prophylaxis.
- ❖ Of those orders that had indications within the guidelines, the majority were also within the guidelines for the dosing regimen. The most common dosing regimen variants from the guidelines included: (1) dosing ondansetron at an 8-hour interval instead of a 12-hour interval for the prophylaxis of delayed CINV; (2) using 8-mg doses instead of 4-mg doses for PONV or prescribing PRN orders for PONV with a short dosing interval (every 4 hours).
- ❖ An important minority of orders fell outside of the guidelines for prescribing indications, with the predominant indication being the treatment of nausea and vomiting of various etiologies. This category of orders also included PRN orders.

Based on the MUE results, the following recommendations from the antiemetic guidelines should be emphasized:

- ❖ For the prophylaxis of delayed CINV, alternative classes of agents (e.g., corticosteroids), when allowed by protocol, may be equally effective. Refer to the NIH antiemetic guidelines for recommendations for alternative regimens for delayed CINV.
- ❖ When ondansetron is utilized for the prophylaxis of delayed CINV, the recommended dosing regimen is 8 mg po every 12 hours x 1–4 days. See NIH antiemetic guidelines for additional information.

- ❖ The recommended dose of ondansetron for the prophylaxis and treatment of PONV is 4 mg administered by IV push.
- ❖ When treating established nausea and vomiting of various etiologies (non-PONV indications), consider alternative antiemetic agents as a first-line treatment approach. 5-HT₃ antagonists should only be used to treat nausea and vomiting when other antiemetic agents have failed, when a patient has unacceptable side effects from other antiemetics, or when other antiemetics are contraindicated. Refer to the NIH antiemetic guidelines for available formulary antiemetic options.
- ❖ PRN dosing of 5-HT₃ antagonists is strongly discouraged.

For additional information regarding antiemetic use, refer to the NIH Clinical Center Antiemetic Guidelines on the NIH CC Pharmacy website (<http://internal.cc.nih.gov/formulary/ccfs/emetic.htm>). Pocket cards of the NIH antiemetic guidelines are also available from the Pharmacy Department.

Memantine (Namenda™): A Brief Review

Memantine was recently approved in the United States for the treatment of moderate-to-severe dementia of the Alzheimer's type.¹ At present, only four agents—all cholinesterase inhibitors—(donepezil, galantamine, rivastigmine, and tacrine) are approved in the United States for treating mild-to-moderate Alzheimer's.

Clinical Pharmacology

Memantine is a low-to-moderate affinity, voltage-dependent, noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor.^{1,2} It also acts as a serotonin 5-HT₃ receptor antagonist with potency similar to that for the NMDA receptor and blocks nicotinic acetylcholine receptors with one-sixth to one-tenth the potency.¹ Memantine has low to no affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine, and glycine receptors and voltage-dependent Ca²⁺, Na⁺, or K⁺ channels.¹

At low doses, memantine appears to reverse deficits of learning and long-term potentiation in subjects with learning deficits.² This is contrary to the expected activity of an NMDA antagonist, since activation of NMDA receptors appears necessary for learning.³ In healthy subjects, NMDA receptor antagonists may inhibit learning and long-term memory.² However, it has been hypothesized that glutamate receptors of the NMDA type are over activated in Alzheimer's disease, with the resulting continuous mild activation resulting in neuronal damage and impairment of learning. Memantine appears able to attenuate this deficit.⁴

In a crossover study enrolling healthy males, administration of memantine 30 mg markedly impaired long-term memory as assessed by recognition performance of objects 80 minutes after initial viewing. Memory testing was initiated after a single oral dose of memantine or placebo.⁵ In another study enrolling healthy volunteers, oral memantine 30 mg

had no effects on mood, attention, concentration, verbal fluency, or short- or long-term memory, but was associated with delayed and reduced conditioned responses which could represent a learning deficit.⁶ It has been suggested that in certain conditions direct tonic activation of NMDA receptors may lead to an increase in synaptic "noise" that may impair association detection. In these conditions, administration of an NMDA receptor antagonist may block the "noise" allowing association and learning.³

In animal models of cerebral ischemia, memantine has been demonstrated to reduce infarct volume, reduce hippocampal and cortical damage, and prevent learning deficits.²

Memantine can block the expression and maintenance of opioid dependence.⁷ In opioid-dependent patients, it attenuated the severity of naloxone-precipitated opioid withdrawal. It may prove useful in the treatment of detoxified opioid-dependent subjects.⁸ This raises the issue of the potential impact of memantine therapy on patients requiring treatment with an opioid. Memantine 30 mg orally did not affect pain or reflex thresholds or monosynaptic or polysynaptic spinal reflexes in 14 healthy volunteers.⁹ Whether it will impact pain control in patients suffering with acute or chronic pain is unknown.

Pharmacokinetics

Peak memantine levels are achieved within 3 to 7 hours following oral administration.^{1,6} Food has no effect on memantine absorption.¹ The mean volume of distribution is 9 to 11 L/kg and plasma protein binding is 45%.¹ Memantine appears to accumulate in the temporal lobe, hypothalamus, and pons at higher concentrations than in other tissues.¹⁰ Levels in the cerebrospinal fluid are lower than those observed in the serum, with a mean CSF to serum ratio of 0.52.¹¹

The terminal half-life ranged from about 60 to 80 hours.^{1,6} Memantine is primarily eliminated in the urine unchanged (57% to 82%).¹ Metabolism of memantine to metabolites is minimal.¹⁰ Three polar metabolites (N-gludantan conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine) demonstrate minimal NMDA receptor antagonist activity.¹ In animal models, hydroxyl derivatives have been identified, but do not appear to cross the blood-brain barrier.¹⁰ In the presence of alkaline urinary pH, the renal excretion and elimination of memantine is substantially reduced compared with that in the presence of acidic urinary pH.¹²

The effects of renal impairment on the pharmacokinetics of memantine have not been assessed. Because memantine is primarily eliminated renally as unchanged drug, it is likely that patients with moderate-to-severe renal impairment will have increased exposure to memantine.¹ The pharmacokinetics of memantine in the young and elderly are similar.¹

Comparative Efficacy

Dementia

A randomized, placebo-controlled study conducted at 32 centers in the United States enrolling 252 community-dwelling patients with advanced Alzheimer's disease (Global Deterioration Scale stage 5 or 6, Functional Assessment Stage

[FAST] greater than or equal to 6a, and Mini-Mental State Examination [MMSE] score 3 to 14) was conducted to evaluate the safety and efficacy of memantine. The study population was 67% women; mean age was 76 years. The mean MMSE score at baseline was 7.9. Patients received memantine 10 mg twice daily or placebo for 28 weeks. The study was completed by 181 patients (72%). The primary efficacy variables were the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-Plus) global score at 28 weeks and the change from baseline to week-28 in the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) modified for more severe dementia (ADCS-ADLsev). If values from the 28-week evaluation were not available, the last observed value was used. Assessments were performed at baseline, week-12, and week-28 or at the time of termination from the study. At week-28, the ADCS-ADL had deteriorated less in the memantine group than in the placebo group (-2.49 vs -5.86, $P=0.003$ for observed cases; $P=0.02$ with last observation carried forward). Improvements were also seen in the CIBIC-Plus (mean difference between groups 0.3; $P=0.06$ with last observation carried forward, $P=0.03$ for observed cases), the Severe Impairment Battery (SIB, mean difference 5.7 units; $P<0.001$ with last observation carried forward, $P=0.002$ for observed cases) and FAST ($P=0.02$ with the last observation carried forward, $P=0.007$ for observed cases) with the memantine therapy. No significant differences between memantine and placebo were observed in the Mini-Mental State Examination score, Global Deterioration Scale stage, or Neuropsychiatric Inventory score. Memantine benefits were observed both in patients with moderate Alzheimer's disease and those with severe Alzheimer's disease. Caregiver time was also reduced in the memantine group (difference between groups 45.8 hours per month, 95% CI 10.37-81.27, $P=0.01$). Adverse events were similar in the two treatment groups.^{1,13,14,15}

A pharmacoeconomic assessment was performed in conjunction with the above study, examining costs from a societal perspective based on data from the 166 patients comprising the treated-per-protocol subset. Caregiver time was reduced in the memantine group (difference 5.15 hours per month, 95% CI -95.27 to -7.17, $P=0.02$). Time to institutionalization ($P=0.052$) and institutionalization at week-28 ($P=0.04$) favored memantine. The total costs from a societal perspective were lower in the memantine group (difference of US \$1,089.74 / month, 95% CI -1,954.90 to -224.58, $P=0.01$), with the primary difference attributed to reduced total caregiver costs (-\$823.77/month, $P=0.03$) and reduced direct nonmedical costs (-\$430.84/month, $P=0.07$). Direct medical costs were higher in the memantine group.¹⁶

Another double-blind, placebo-controlled study conducted in the United States assessed memantine added to therapy with donepezil in patients with moderate-to-severe Alzheimer's disease (MMSE of 5 to 14). The study enrolled 404 patients at 37 sites. Patients had been treated with donepezil for at least 6 months at stable doses of 5 to 10 mg/day for at least 3 months and throughout the study.

Memantine 10 mg twice daily or placebo was administered for 24 weeks. Results for the SIB (mean difference 3.3 units; $P<0.001$), ADCS-ADL (mean difference 1.6 units, $P<0.05$), ADCS-ADLsev ($P=0.028$), Rating Scale for Geriatric Patients (BGP) Care Dependence Subscale, and CIBIC-Plus ($P=0.027$) favored memantine. Improvement related to baseline was reported for the memantine/donepezil group, while those in the placebo/donepezil group demonstrated a progressive decline.^{1,17}

Additional studies are currently ongoing in the United States, including studies enrolling patients with mild-to-moderate and moderate-to-severe Alzheimer's disease and patients receiving concomitant therapy with a cholinesterase inhibitor.

In Europe, memantine is manufactured and marketed by Merz Pharmaceuticals. Several additional studies have been conducted in Europe. One is a randomized, double-blind, placebo-controlled study that assessed memantine in 579 patients with mild-to-moderate vascular dementia and MMSE scores of 10 to 22. This study was conducted in the United Kingdom. Patients were treated with memantine 10 mg twice daily or placebo for 28 weeks. Intent-to-treat analysis included 548 patients with at least one post-baseline efficacy assessment. An advantage for memantine was observed in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), with the greatest benefit observed in patients with a pretreatment MMSE less than 15. The change in ADAS-Cog from baseline differed by a mean of -1.75 points (95% CI -3.023 to -0.49) between the two groups. A difference in favor of memantine was also observed for the Nurses' Observation Scale for Geriatric Patients memory dimension ($P=0.02$). No difference was observed with the Clinical Global Impression of Change (CGI-C) assessment. Adverse effects occurred with similar frequency.^{18,19} Another similar study was conducted in France and enrolled 321 patients with mild-to-moderate vascular dementia. In the intention-to-treat population (consisting of 288 patients with at least one post-baseline efficacy assessment), the ADAS-Cog improved by a mean of 0.4 points in the memantine group, but declined by 1.6 points in the placebo group (95% CI 0.49-3.6 for the difference, $P=0.005$). The greatest improvement was observed in patients with a baseline MMSE less than 15. The MMSE ($P=0.003$), Gottfries-Brane-Steen intellectual function subscores ($P=0.04$), and Nurses' Observation Scale for Geriatric Patients disturbing behavior dimension ($P=0.07$) also demonstrated an advantage for memantine. The frequency of adverse events was similar in the two groups.^{20,21}

Memantine was also assessed in a randomized, double-blind placebo-controlled study conducted in Latvia enrolling 167 care-dependent inpatients with moderately severe-to-severe primary dementia (DSM-III criteria for dementia, Global Deterioration Scale stages 5-7, MMSE score less than 10). Patients received memantine 5 mg/day for the first weeks then 10 mg/day for the next 11 weeks (82 patients), or placebo (84 patients). One patient did not receive study medication and was excluded from the analysis. The Clinical

Impression of Improvement demonstrated a difference in favor of memantine at both the 4- and 12-week assessments. Response (improvement) occurred in 59% of memantine-treated patients and 40% of placebo-treated patients at week-4, and 73% of memantine-treated patients and 45% of placebo-treated patients at week-12 ($P < 0.001$). The Behavioral Rating Scale for Geriatric Patients 'care dependence' subscores also improved to a greater extent in the memantine group (change at visit-5 compared to visit-1: -3.1 with memantine vs -1.1 with placebo; $P = 0.016$). BGP 'care dependence' response (defined as a 15% or greater improvement of the subscores from baseline) occurred in 65.3% of memantine-treated patients compared with 39.5% of placebo-treated patients.²²

Several other smaller studies were also conducted in Germany, where memantine has been available for more than 10 years. In one randomized, placebo-controlled study enrolling 88 patients with mild-to-moderate dementia, memantine 20 mg/day was more effective than placebo as assessed by the Sandoz Clinical Assessment Geriatric Scale (SCAG, a global assessment of change in the patients' condition) and the GBS Scale (a behavioral assessment). Memantine was also associated with improvement in carrying out activities of daily living. Based on physician global assessment, improvement was reported for 26.8% of placebo-treated patients and 58.5% of memantine-treated patients. Worsening condition was reported more frequently in the placebo group by all assessments.²³ In another double-blind, placebo-controlled trial enrolling 66 patients with mild-to-moderate vascular dementia, memantine was associated with greater improvement than placebo on the SCAG total score and the SCAG subscales of cognitive disturbances, lack of drive, emotional disturbances, social behavior, and somatic disturbances. A difference from placebo was observed within 14 days of initiating therapy. Memantine also improved performance in carrying out activities of daily living and improvement in general health and disease symptomatology as assessed by the physician's global assessment.²⁴

A placebo-controlled study enrolling geriatric inpatients evaluated the impact of memantine therapy in 30 patients with chronic central nervous system diseases. Patients had been hospitalized for at least 2 years and had the following symptoms: senile reduction in mental performance, attention disturbances, fatigue, sleep disturbances, anxiety, affective disturbances, psychomotor disturbances, and confusion (disorientation to time and place). Patients received either placebo or memantine for 6 weeks. Improvement in the memantine-treated patients was observed as assessed by psychiatric rating scale and psychometric tests of attention, vigilance, short-term memory, and intelligence (flicker-frequency analysis-stress value, digit span, mosaic test).²⁵

An ongoing double-blind, placebo-controlled study enrolling 140 patients is currently assessing memantine in the treatment of AIDS Dementia Complex. Patients received placebo or memantine at escalating doses from 10 mg to 40 mg during the first 4 weeks and then 40 mg or the maximum

tolerated dose through week-16. The double-blind phase is being followed by a 4-week washout period and then a 60-week open-label memantine study.²⁶

A case report also described the use of memantine in the therapy of a patient with alcohol dementia and chronic alcoholism. After 5 weeks therapy, improvement in MMSE and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Verbal Fluency, CERAD Wordlist Recall, and CERAD Drawing were observed.²⁷

Parkinson's Disease

A crossover study assessed memantine in 12 patients with idiopathic Parkinson's disease with motor fluctuations ("wearing off" and the need for 4 or more daily levodopa doses) and drug-induced dyskinesias. Memantine or placebo was administered in conjunction with their existing therapy. Memantine was initiated at a dose of 10 mg/day and titrated over the first week to 30 mg/day, then continued at that dose for the second week. Memantine produced improvement on the Unified Parkinson's Disease Rating Scale motor score during both "off" and "on" states. Memantine also produced a greater effect than placebo on the resting tremor score ($P < 0.02$) and bradykinesia score ($P < 0.03$) in the "off" state. Memantine had no effect on drug-induced dyskinesias or on levodopa effect latency or effect duration.²⁸

In another study, 14 patients with idiopathic Parkinson's disease with motor fluctuations on levodopa were treated with open-label adjunctive memantine 30 mg/day. Therapy was initiated at a dose of 5 mg twice daily and titrated over the first week to 10 mg three times daily. Ten patients completed 1 month of therapy, 5 of whom experienced improvement in the main parkinsonian features (rigidity, bradykinesia, tremor, gait, and postural reflexes, improvement by 1 or more points on the Webster scale). Six patients experienced improvement in "off" episodes (daily mean of 273 minutes to 172 minutes). Dyskinesias did not improve.²⁹

A case report described reduction in "on" phase dyskinesias and motor fluctuations with memantine therapy in a 35-year-old male with a 14-year history of Parkinson's disease and severe peak-dose dyskinesias. "Off" phase dystonias were not reduced.³⁰

Neuropathy

The effects of memantine in the treatment of neuropathic pain were evaluated in a randomized, double-blind, crossover study enrolling 19 patients with chronic pain following amputation or surgery. Patients received 5 weeks of therapy with memantine or placebo, followed by a 4-week washout period, and then 5 weeks of therapy with the alternate agent. The memantine dose was titrated from 5 to 20 mg/day. At a dose of 20 mg/day, memantine did not reduce spontaneous or evoked pain in this population.³¹ Similarly in a study of memantine 30 mg/day compared with placebo in 36 patients with chronic phantom limb pain, mean pain relief did not differ between the groups.³²

In another crossover study enrolling 23 patients with diabetic neuropathy and 21 patients with postherpetic neuralgia, memantine was no more effective than placebo.³³

Contraindications

Memantine is contraindicated in patients with known hypersensitivity to the drug or any component of the product formulation: microcrystalline cellulose, lactose monohydrate, colloidal silicon dioxide, talc, magnesium stearate, hypromellose, triacetin, titanium dioxide, FD & C yellow #6 or FD & C blue #2 (5 mg tablet) or iron oxide black (10 mg tablet).¹

Warnings and Precautions

Conditions that increase urine pH may decrease the elimination of memantine resulting in increased plasma levels and potentially increased adverse effects.¹

Memantine has not been assessed in patients with seizure disorders. In clinical trials seizures occurred in 0.2% of memantine-treated patients and 0.5% of placebo-treated patients.¹

Memantine exposure is expected to be increased in patients with renal impairment. Dosage adjustments should be considered; use in patients with severe renal impairment is not recommended.¹

Memantine is in Pregnancy Category B. Teratogenic effects were not observed in animal studies. Slight maternal toxicity and reduced pup weights were observed. Memantine should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.¹

It is not known if memantine is excreted in breast milk. It should be used with caution in nursing mothers.¹

No studies have been conducted to assess the safety or efficacy of memantine for any pediatric indications.¹

Adverse Reactions

Adverse effects reported during memantine therapy in patients with dementia have included headache, dizziness, akathisia, insomnia, restlessness, increased motor activity, excitement, and agitation.^{23,24} Many of these symptoms decline with continued therapy and can be lessened with a longer dosage titration.²⁴ Most adverse effects have occurred with similar frequency in the memantine- and placebo-treated patients.¹⁷ Adverse effects occurring in at least 2% of patients receiving memantine, and more frequently in memantine-treated patients than placebo-treated patients, are summarized in Table 1.¹

Other adverse events occurring in at least 2% of patients, but no more frequently than with placebo, included agitation, falls, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, gait abnormality, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.¹

Memantine has been reported to cause psychosis in Parkinson's disease in some patients at doses lower than those necessary to produce improvement in parkinsonian symptoms.³⁴

Memantine had minimal abuse potential in animal models. Abuse has not been reported in clinical practice.^{1,3}

Table 1: Adverse Effects Occurring in at Least 2% of Patients Receiving Memantine, and More Frequently with Memantine than Placebo¹

Adverse Event	Placebo (n=922)	Memantine (n=940)
Dizziness	5%	7%
Confusion	5%	6%
Headache	3%	6%
Constipation	3%	5%
Coughing	3%	4%
Hypertension	2%	4%
Back pain	2%	3%
Hallucinations	2%	3%
Pain	1%	3%
Somnolence	2%	3%
Vomiting	2%	3%
Dyspnea	1%	2%
Fatigue	1%	2%

Drug Interactions

In vitro and in animal models, memantine did not reduce the anticholinesterase activity of the cholinesterase inhibitors donepezil, galantamine, or tacrine, suggesting it should not reduce the activity of these agents used in the therapy of Alzheimer's disease.^{1,35} In a German postmarketing surveillance assessment, data were collected on 158 patients receiving concomitant memantine (median 20 mg/day) with a cholinesterase inhibitor (most commonly donepezil, 84%). In approximately half of the patients, the cholinesterase inhibitor was initiated first, with memantine therapy added. In another 42%, memantine therapy was initiated first, with the cholinesterase inhibitor added later. In only 11 patients (8%) were the agents initiated concurrently. Over an average observation period of 4 months on stable doses of both medications, the combination was reported to be well tolerated in 98% of patients. Adverse effects resolved without sequelae and did not require discontinuation of therapy.³⁶

Concomitant administration with donepezil did not affect the pharmacokinetics of either agent.¹

Memantine has not been assessed in combination with other NMDA antagonists (amantadine, ketamine, dextromethorphan). These agents should be used concomitantly with caution.¹

Memantine produces minimal inhibition of CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4 and is not expected to produce drug interactions with agents metabolized by these enzymes.¹ Since memantine undergoes minimal metabolism, an interaction between memantine and agents that are inhibitors of these enzymes is unlikely.¹

Memantine is eliminated in part by tubular secretion. Concomitant use of other agents that use the same renal cationic system (e.g., hydrochlorothiazide, triamterene, cimetidine, ranitidine, quinidine, and nicotine) could result in altered

plasma levels of both agents.¹ Multiple doses of hydrochlorothiazide/triamterene did not affect the area under the curve (AUC) of memantine at steady-state. Memantine did not alter the bioavailability of triamterene and was associated with only a 20% reduction in the hydrochlorothiazide peak and AUC.¹

Memantine clearance is reduced about 80% under alkaline urine conditions (pH 8). Alterations of urine pH toward alkaline may lead to an accumulation of memantine. Agents that alkalinize the urine such as carbonic anhydrase inhibitors and sodium bicarbonate are expected to reduce the renal elimination of memantine, as may some medical conditions (renal tubular acidosis, severe urinary tract infections).¹

Dosing

The dosage demonstrated to be effective in clinical trials is 20 mg/day. The recommended starting dose is 5 mg once daily. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice daily), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice daily). The minimal interval between dose increases is 1 week.¹ A reduced dose should be considered in patients with moderate renal impairment.¹

Memantine can be taken with or without food.¹

Product Availability

Memantine received FDA approval in October 2003. Memantine has been available in Germany for more than 10 years. It was approved in the entire European Union in 2002.³⁷ The compound was developed by Merz Pharmaceuticals in Germany and has granted exclusive marketing rights in the United States to Forest Laboratories Inc. It is available as 5 mg and 10 mg tablets, in bottles of 60, 200, and 2000 and unit-dose packages of 100, as well as a dose-titration pack containing 49 tablets (28 5 mg tablets and 21 10 mg tablets).¹

Memantine should be stored at 25°C (77°F) with excursions permitted to 15 to 30°C (59 to 86°F).¹

Conclusion

Memantine appears to offer some benefit in slowing the decline observed in Alzheimer's disease and possibly improving function in activities of daily living. Additional studies are necessary to determine if any benefits are observed in patients with Alzheimer's disease already receiving cholinesterase inhibitors.

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Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- ❖ Fosamprenavir (Lexiva), an oral antiretroviral [prodrug of amprenavir]
- ❖ Memantine (Namenda), an oral NMDA receptor antagonist for treatment of Alzheimer's

Deletions

- ❖ Dactinomycin

FDA Safety Alerts

- ❖ You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to www.fda.gov and click on "MedWatch." MedWatch is the FDA's medical products reporting program.
- ❖ You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to fdalists@archie.fda.gov. In the message body enter: *subscribe medwatch* and your e-mail address.

Drug Information Service

- ☛ Patient-specific pharmacotherapy evaluation and management
- ☛ Comprehensive information about medications, biologics, and nutrients
- ☛ Critical evaluation of drug therapy literature
- ☛ Assistance with study design and protocol development
- ☛ Clinical trial drug safety monitoring
- ☛ Investigational drug information
- ☛ Parenteral nutrition assessment and management

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