



Pharmacy

January/February 1998

Update

Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor

Karim Anton Calis, Pharm.D., M.P.H.
Coordinator, Drug Information
Service, and Endocrinology Clinical
Pharmacy Specialist
kcalis@nih.gov

Associate Editor

Amy M. Heck, Pharm.D.
Specialized Resident in Drug
Information Practice and
Pharmacotherapy
aheck@nih.gov

In This Issue

- Donepezil (Aricept™):
A Brief Review
- Terbinafine (Lamisil®):
A Brief Review
- Drug-Nutrient
Interactions
- Did You Know . . .
- Formulary Update

Donepezil (Aricept™): A Brief Review

Donepezil (Aricept™) is a centrally acting, reversible acetylcholinesterase inhibitor recently approved by the FDA for the treatment of mild to moderate Alzheimer's disease (AD). It is the second drug to be approved for the treatment of AD and offers several advantages over tacrine (Cognex®).

Description: Aricept™ is marketed by Eisai and is available as 5-mg and 10-mg tablets.

Indication: Aricept™ is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

Pharmacology: Donepezil enhances cholinergic function by inhibiting neuronal acetylcholinesterase and increasing acetylcholine concentrations in the brain. It is highly selective for central nervous system acetylcholinesterase, with less peripheral activity and a longer duration of inhibitory action than tacrine. The effects of donepezil may decrease as the disease progresses and fewer cholinergic neurons remain functional. As a result, donepezil does not alter the progression of AD.

Pharmacokinetics: Donepezil is well absorbed after oral administration, with a relative bioavailability of 100 percent. Peak plasma concentrations are achieved within 3 to 5 hours. Food appears to have no effect on the pharmacokinetics of donepezil. Approximately 96% of donepezil is bound to plasma proteins (75% to albumin and 21% to alpha acid glycoproteins). The steady-state volume of distribution is 12 L/kg, and a larger volume of distribution has been reported in elderly subjects as compared to young healthy subjects. Steady-state serum concentrations are achieved in 15 days, and the elimination half-life is approximately 70 hours. Although elderly subjects have exhibited a larger volume of distribution and longer half-life, dosing adjustments do not appear to be necessary in these patients.

Donepezil is extensively metabolized in the liver by oxidation via the cytochrome P450 2D6 and 3A4 isoenzymes and glucuronidation. Four major metabolites have been identified. The 6-O-desmethyl-donepezil metabolite has acetylcholinesterase inhibitory activity similar to that of the parent compound. Donepezil is excreted in the urine as unchanged drug and in the form of urinary metabolites.

Selected Clinical Studies: The efficacy of donepezil for the treatment of AD has been demonstrated in randomized, double-blind, placebo-controlled clinical trials. Each trial utilized the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) to examine elements of memory, orientation, attention, reasoning, language, and praxis to measure cognitive performance.

In a phase III trial, 450 patients were randomized to receive donepezil 5 mg, donepezil 10 mg, or placebo for 6 months in a double-blinded active treatment phase. This phase was followed by a 6-week washout period. Patients in both treatment groups experienced statistically significant improvements in cognitive function based on ADAS-cog scores. In addition, global performance improvement, as measured by the Clinician's Interview-based Impression of Change incorporating caregiver input (CIBIC-plus), was significantly greater in the donepezil treatment groups compared to placebo. Donepezil also reduced the number of treatment failures by up to 44% based on CIBIC results. There was no statistically significant difference between the donepezil 5-mg and 10-mg treatment groups. Following the 6-week placebo washout period, ADAS-cog scores for both donepezil treatment groups were similar to scores of the placebo treatment group. These results suggest an abatement of the beneficial effects of donepezil after 6 weeks.

In a 15-week study, patients were randomized to receive 5 mg of donepezil, 10 mg of donepezil, or placebo for 12 weeks followed by a 3-week placebo washout period. As in the 30-week trial, patients receiving active treatment showed a statistically significant improvement in ADAS-cog scores. A significant difference was not found between the 5-mg and 10-mg donepezil treatment groups, and during the placebo washout period, cognitive function declined in both active treatment groups as demonstrated by increases in ADAS-cog scores. Results of CIBIC-plus scores demonstrated greater improvement in the active treatment groups compared to the placebo group.

Adverse Effects: The most common adverse effects reported in patients taking donepezil are nausea, vomiting, diarrhea, gastric upset, dizziness, muscle cramps, fatigue, anorexia, and headache. These adverse effects are related to the cholinergic activity of donepezil and are often mild to moderate in intensity. Many of the adverse reactions reported in clinical trials were transient and often resolved spontaneously with continued donepezil therapy. Cardiovascular effects reported with donepezil, occurring in at least 1% of patients include hypertension, vasodilation, atrial fibrillation, hot flashes, and hypotension. Bradycardia and syncope have also occurred during treatment in some patients with AD. However, significant changes in blood pressure, heart rate, or clinical laboratory tests were not observed. Hepatotoxicity has not been observed in patients receiving donepezil.

Drug Interactions: Since donepezil is metabolized by CYP2D6 and CYP3A4, there is the potential for interactions with substrates, inducers, and inhibitors of these isoenzymes. However, *in vitro* studies have shown that donepezil's affinity for these enzymes is low, and the manufacturer suggests there is little likelihood of interference with other drugs metabolized by this system. Inhibitors of CYP450 2D6 and 3A4 isoenzymes have been shown to inhibit the metabolism of donepezil *in vitro*. However, further study is needed to evaluate the clinical significance of this observation. Inducers of these isoenzyme systems (e.g., phenytoin, carbamazepine, dexamethasone, rifampin and phenobarbital) may increase the rate of elimination of donepezil.

Due to opposing mechanisms of action, donepezil may interfere with the activity of anticholinergic medications. In addition, donepezil may have a synergistic effect when given with succinylcholine or other cholinergic agonists such as bethanechol.

Precautions/Contraindications: Donepezil is contraindicated in patients with known hypersensitivity to the drug or to other piperidine derivatives. No dosage adjustments appear to be necessary in the elderly or in patients with renal disease. In patients with hepatic disease, a study comparing 10 patients with stable alcoholic cirrhosis to 10 healthy age- and sex-matched subjects showed a 20% decrease in the clearance of donepezil in patients with cirrhosis. Cholinesterase inhibitors, such as donepezil, should be prescribed with caution to patients with sick-sinus syndrome or other cardiac conduction abnormalities, asthma, seizures, active gastrointestinal disease, or in patients receiving non-steroidal antiinflammatory agents.

Dosage and Administration: The recommended dose of donepezil for patients with mild to moderate AD is 5 mg daily administered in the evening. The use of 10 mg daily has shown greater benefit in some patients. To minimize the occurrence of cholinergic adverse effects, it is important to administer donepezil at a dose of 5 mg per day for at least 4 to 6 weeks before increasing the dose to 10 mg daily. Donepezil may be taken without regard to food.

Medication	Dose	Monthly Cost*
Donepezil (Aricept™)	5 mg daily	\$72
	10 mg daily	\$72
Tacrine (Cognex®)	10 mg four times daily	\$70
	20 mg four times daily	\$70
	30 mg four times daily	\$70
	40 mg four times daily	\$70

*Based on Federal Supply Schedule

Cost: The total cost of tacrine therapy must include costs incurred from weekly monitoring of liver function. The manufacturer of tacrine recommends liver function be monitored weekly for the first 18 weeks of therapy followed by testing every 3 months thereafter. In addition, weekly monitoring of liver function is recommended for 6 weeks whenever the dose of tacrine is increased.

Conclusion: Donepezil appears to be effective for the treatment of mild to moderate Alzheimer's dementia. Donepezil offers clear advantages compared to tacrine. These include once-daily dosing, fewer adverse effects, and a lower potential for drug interactions.

References available upon request.

Terbinafine (Lamisil®): A Brief Review

Onychomycosis, dermatophyte fungal infections of the fingernail and toenail, is a common disorder affecting approximately 2.5% of the population. Terbinafine (Lamisil®) is the first antifungal agent of the allylamine class approved for the treatment of onychomycosis.

Description: Terbinafine (Lamisil®) is marketed by Novartis Pharmaceuticals and is available as 250-mg tablets and a 1% topical cream.

Indication: Terbinafine is indicated for the treatment of onychomycosis of the toenail and fingernail due to dermatophytes.

Pharmacology: Terbinafine exerts fungicidal activity by selectively inhibiting squalene epoxidase, a key enzyme involved in fungal cell-membrane synthesis. Inhibition of squalene epoxidase causes ergosterol deficiency and accumulation of cytotoxic saqualene within the fungal cell thereby resulting in cell death. Terbinafine is active against most strains of *trichophyton mentagrophytes* and *trichophyton rubrum*.

Pharmacokinetics: Terbinafine is well absorbed, with an oral bioavailability of approximately 70%. Peak plasma concentrations are achieved within 2 hours after a single

dose, and the absorption of terbinafine is enhanced when the drug is taken with food. Terbinafine is greater than 99% bound to plasma proteins and is well distributed to the sebum and skin. Terbinafine is eliminated slowly from the skin and adipose tissue, with a terminal elimination half-life of approximately 100 hours. In patients who have been taking terbinafine for several weeks, the elimination half-life may be prolonged. After one month of oral terbinafine therapy, nail concentrations remain detectable for up to 3 months. Terbinafine is extensively metabolized by the liver, and 90% of the drug is eliminated in the urine as inactive metabolites.

Selected Clinical Studies: Several studies have evaluated the efficacy of terbinafine for the treatment of various dermatophytoses, including infections of the scalp, skin, groin, nails, and feet. The role of terbinafine in the treatment of onychomycosis was established by several placebo-controlled clinical trials. In a large multicenter, placebo-controlled trial, 250 mg of terbinafine daily for 12 weeks was found to be effective in achieving a successful clinical outcome in 74% (n = 385) of patients with toenail onychomycosis. Additionally, terbinafine has been shown to be more effective than griseofulvin for the treatment of onychomycosis, with the advantage of shorter treatment regimens (12 weeks for terbinafine versus 24-52 weeks for griseofulvin).

Several studies have evaluated the comparative efficacy of terbinafine and itraconazole for the treatment of onychomycosis. Brautigam and colleagues conducted a multicenter, double-blind, randomized trial in 195 patients with toenail tinea. Subjects were randomized to receive either 200 mg of itraconazole daily or 250 mg of terbinafine daily for 12 weeks. Mycological cure rates were 81% for the terbinafine group and 63% for those who received itraconazole. In a similar study of 372 patients with toenail onychomycosis, the mycological cure rate for terbinafine-treated patients was 73% and 45.8% for those treated with itraconazole.

Intermittent terbinafine therapy for the treatment of toenail onychomycosis has also been evaluated. Tosti and colleagues performed an open-label, randomized four-month trial of continuous terbinafine (250 mg daily), intermittent terbinafine (500 mg daily for one week every month), and intermittent itraconazole (400 mg daily for one week every month). Six months after discontinuation of treatment, the mycological cure rates for those who received continuous terbinafine, intermittent terbinafine, and intermittent itraconazole were 94.1%, 80%, and 75%, respectively.

Adverse Effects: During controlled clinical trials, adverse events associated with terbinafine were reported to be mild and transient. These included diarrhea (5.6%), abdominal pain (2.4%), rash (5.6%), pruritus (2.8%), urticaria (1.1%), elevation in hepatic transaminases (3.3%), and taste disturbances (2.8%). Rare cases of retinal and ocular lens changes have been reported. Data collected from four post-marketing surveillance studies including over 25,000 patients reported the overall incidence of adverse effects to be 10.5%. In this report, 11 serious adverse events were noted, including two patients who presented with hepatobiliary dysfunction. Because transient decreases in absolute lymphocyte count have been reported, precautions should be taken in immunocompromised patients receiving therapy for greater than six weeks. In addition, hepatic function tests should be

monitored when treatment duration exceeds 6 weeks.

Drug Interactions: Although terbinafine is metabolized by the liver, it does not undergo oxidation by the cytochrome P450 system. Therefore, the potential for interactions with other medications metabolized by this system is minimal. *In vivo* drug interaction studies of terbinafine in normal volunteers showed that clearance of antipyrine, digoxin, terfenadine, and warfarin was not altered. Terbinafine increases the clearance of cyclosporine by approximately 15%. Additionally, rifampin increases the clearance of terbinafine by 100%, while cimetidine decreases its clearance by 33%.

Dosage and Administration: The dose of terbinafine for the treatment of onychomycosis of the fingernail and toenail is 250 mg once daily for six weeks and 250 mg once daily for twelve weeks, respectively.

Medication	Regimen	Cost*
Itraconazole (Sporanox®)	200 mg once daily for 12 weeks	\$581.22
Terbinafine (Lamisil®)	250 mg once daily for 12 weeks	\$292.06

*Based on Federal Supply Schedule

Conclusion: Terbinafine is more effective than griseofulvin and itraconazole for the treatment of dermatophyte nail infections. Additionally, terbinafine is cost-effective, well tolerated, and appears to have a low potential for drug interactions.

References available upon request.

Drug-Nutrient Interactions

A new hospitalwide program for educating patients who receive medications which have the potential for serious drug-nutrient interactions was approved by the Pharmacy and Therapeutics Committee. The following Clinical Center formulary medications have been targeted based upon their potential for serious drug-nutrient interactions:

Drug	Potentially Interacting Nutrient
Selegeline	tyramine
Phenelzine	tyramine
Tranlycypromine	tyramine
Lithium	sodium
Warfarin	vitamin K
Cisapride	grapefruit products
Amlodipine	grapefruit products
Nifedipine	grapefruit products
Verapamil	grapefruit products
Cyclosporine	grapefruit products
Theophylline	grapefruit products

Patients who receive one or more of these medications will be identified using an automated drug-nutrient interactions alert generated by the Clinical Center's Medical Information System (MIS). At the time of order entry, the prescriber will be informed of the potential for a drug-nutrient interaction. Patient evaluation and education will be provided by a dietitian, nurse, or pharmacist.

Did You Know . . .

- ❖ Life-threatening irregular heart rhythms may result when serum concentrations of astemizole (Hismanal®) are elevated. This can occur with high doses of astemizole or when it is combined with mibefradil, clarithromycin, troleandomycin, indinavir, ritonavir, saquinavir, nelfinavir, fluoxetine, paroxetine, fluvoxamine, nefazodone, sertraline, or zileuton. Astemizole should not be taken with grapefruit juice.
- ❖ Sibutramine (Meridia®, Hoffman-La Roche), a norepinephrine and serotonin reuptake inhibitor, was recently approved for the management of obesity.
- ❖ A public health advisory was issued by the FDA describing reports of epidural and spinal hematomas with the concurrent use of low molecular weight heparin (LMWH) and spinal/epidural anesthesia or spinal puncture. Although the 30 reported cases were in patients treated with enoxaparin (Lovenox®), the potential for this adverse event to occur with other LMWHs or heparinoids exists.
- ❖ Influenza activity in the U.S. increased from mid-December through early January. Two new strains of influenza A viruses (A/Nanchang/933/95—like and A/Sydney/05/97—like) have been identified.
- ❖ Becaplermin (Regranex Gel®), a recombinant human platelet-derived growth factor for topical administration, was recently approved for the treatment of lower extremity diabetic neuropathic ulcers.

Formulary Update

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

Additions:

- ❖ Topiramate (Topamax®) tablets, an antiepileptic agent.
- ❖ Levofloxacin (Levaquin®) tablets and injection, a fluoroquinolone antibiotic.
- ❖ Delavirdine (Rescriptor®) tablets, a non-nucleoside reverse transcriptase inhibitor for the treatment of HIV-1 infection in combination with other antiretroviral agents.
- ❖ Azithromycin for intravenous use (Zithromax I.V.®), a macrolide antibiotic.
- ❖ Troglitazone (Rezulin®) tablets, a thiazolidinedione derivative for the treatment of Type-2 diabetes.

- ❖ Sodium sulfacetamide lotion (Sulfacet-R®), a topical sulfonamide for the treatment of acne and seborrheic dermatitis.
- ❖ Famciclovir (Famvir®) tablets, an antiviral agent for the treatment of herpes zoster and genital herpes.
- ❖ Midodrine HCl (ProAmantine®), an alpha₁-selective agonist for the management of symptomatic hypotension.
- ❖ Tobramycin sulfate for inhalation (TOBI™), use of this product is restricted for pulmonary infections in patients with cystic fibrosis.
- ❖ Morphine oral solution 2 mg/mL, a dilute solution for use in pediatric patients.
- ❖ Tetracaine HCl for injection, a local anesthetic.

Deletions:

- ❖ Valacyclovir (Valtrex®)
- ❖ Flavoxate (Urispas®)
- ❖ Sebutone® shampoo
- ❖ Mycolog® cream and ointment
- ❖ Nystatin oral tablets
- ❖ Streptokinase injection
- ❖ Pyridostigmine (Mestinon®)

Editor's Note

We wish to thank Christine Chamberlain, Pharm.D. and Denise Ford, M.S., R.D. for their contributions to this issue of *Pharmacy Update*.

Drug Information Service

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

496-2407

Pager #104-2619-7 or 104-4152-7

Building 10, Room 1N-257



**Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196**