

NEW DRUG UPDATE

March 2002

Volume VIII, Issue 2



Robert C. Byrd Health Sciences Center of West Virginia University ? Charleston Division
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Reminyl® (galantamine hydrobromide)

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Introduction

Reminyl® [galantamine hydrobromide (gal-AN-ta-meen)] was approved by the FDA in February 2001 for the treatment of mild to moderate dementia of the Alzheimer's type. Galantamine is postulated to exert its effect by enhancing cholinergic function through a competitive and reversible inhibition of acetylcholinesterase in the CNS.

Therapeutic Recommendation

Galantamine is a new cholinesterase inhibitor that decreases the degree of cognitive impairment in mild to moderate stages of Alzheimer's disease. Galantamine has been proven safe and effective in randomized placebo controlled trials. It significantly improves cognition and global function as measured by the Alzheimer's Disease Assessment Scale and the Clinician's Interview Based Impression of Change over placebo. Current trials indicate that it is effective for at least six months. At twelve months, cognitive function does not significantly deviate from baseline.

Galantamine compares well with its competitors that are already marketed. The price is similar to its major competitors. There is no evidence of hepatotoxicity, which is seen with tacrine. Galantamine is dosed twice daily which may be a disadvantage regarding compliance. Aricept is a once daily drug, which is comparable in price to galantamine. The adverse effect profile seen with galantamine is very similar to its competitors. Galantamine also has a liquid formulation, which allows for easier administration to patients who are not able to tolerate tablets. Galantamine is most effective in the moderate stages of the disease due to the ability to measure effectiveness better with assessment scales. Clinically, assessment scales, such as those listed previously, show a high extent of variability on retesting over time, and are not considered a good monitoring tool for effectiveness outside of clinical trials. The best way to monitor effectiveness in this patient population is from the caregivers who can assess their global change, functional abilities, and behavior, since the caregivers see the patients on an everyday basis. Overall, galantamine is a good agent to be used to treat the cognitive impairments associated with Alzheimer's disease patients.

**Inside
This
Issue:**

? Reminyl® (galantamine)

? Penlac® (ciclopirox)

Dosing and Administration

Galantamine is available in circular biconvex film-coated tablets of 4 mg (off white), 8 mg (pink), and 12 mg (orange brown). Each strength is supplied in bottles of 60 tablets. It is also available as a 4 mg/mL oral solution, which comes as a clear colorless solution supplied in 100 mL bottles with a calibrated pipette. Galantamine should be administered twice a day, preferably with morning and evening meals.

The recommended starting dose is 4 mg twice daily (8 mg/d). After a minimum of four weeks of treatment, if dose is tolerated, then the dose should be increased to 8 mg twice daily (16 mg/d). Further increases to 24 mg/d and 32 mg/d can be made, but only after a minimum of four weeks at the previous dose has been attempted and tolerated. The dose is titrated slowly to help decrease the incidence of adverse effects that occur at the higher doses. The dose shown to be effective in controlled clinical trials is 16-32 mg/d given twice daily. However, the recommended dose range is 16-24 mg/d given twice daily with possible additional benefit with the 24-mg/d regimen.

Contraindications

Galantamine is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulation.



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Physician's Guide to
Newly Released
Medications...**

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Cost Comparison

Medication/Dose	Cost*		
	<u>Drug Emporium</u>	<u>Kroger</u>	<u>Rite Aid</u>
Reminyl® 8 mg BID	128.05	150.09	177.99
Exelon® 3 mg BID	136.59	155.29	159.29
Aricept® 5 mg QD	127.46	150.99	140.00
Cognex® 20 mg QID	154.09	176.39	207.00

*Prices represent cost to the patient for a thirty -day supply

Special populations

Hepatic Disease: In mild hepatic impairment, the pharmacokinetic properties were similar to those of healthy subjects. In moderate hepatic impairment, the clearance was decreased by 25 %, thus dose titration should proceed cautiously. Galantamine should be avoided in patients with severe hepatic impairment.

Renal Disease: In moderately impaired renal function, the AUC is increased by 37 %, thus dose titration should proceed cautiously. The use of galantamine is not recommended in patients with severe renal impairment (CL_{cr} < 9 mL/min).

Geriatrics: Following usual dosing, the data from clinical trials showed that concentrations were 30 to 40 % higher than in young healthy subjects. The clinical trials were done mostly in the elderly population, so a dose adjustment would not be necessary.

Gender and Race: Although the effects of gender and race were not specifically studied, it was found that the clearance was about 20 % lower in females than males. Race had no effect on the clearance of galantamine.

Pregnancy: Galantamine is classified as pregnancy category B, meaning that there are no human studies to prove safety and efficacy during pregnancy, but animal studies demonstrate no evidence of teratogenicity.

Lactation: It is unknown whether galantamine is excreted into human breast milk. Currently there is no indication for use in nursing mothers.

Pediatrics: There are no clinical trials demonstrating safety and efficacy in children, therefore it is not recommended for children.

Drug Interactions

Metabolism of galantamine is mainly through the cytochrome P450 system with CYP2D6 and CYP3A4 being the major isoenzymes involved. Galantamine did not affect the pharmacokinetics of warfarin or digoxin when administered concomitantly. The inhibitory potential on the major forms of the cytochrome P450 system is very low.

Anticholinergics: Anticholinergic medications interfere with the activity of galantamine by blocking acetylcholine receptors where the additional acetylcholine would bind due to the enzyme, acetylcholinesterase, being inhibited. Galantamine also has the potential to interfere with the activity of anticholinergic medications.

Cholinomimetics/Cholinesterase Inhibitors: A synergistic effect is expected when cholinesterase inhibitors are given with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents, or cholinergic agonists.

Cimetidine: It can increase the bioavailability of galantamine by approximately 16 %.

Ketoconazole: It can increase the AUC of galantamine by 30 %.

Erythromycin: It can increase the AUC of galantamine by 10 %.

Paroxetine: It can increase the oral bioavailability of galantamine by as much as 40 %.

Common Adverse Drug Reactions

The most frequent adverse events, occurring in at least five percent of the population, leading to discontinuation were nausea, vomiting, anorexia, dizziness, and syncope. Other common side effects, occurring in at least 2 percent of the patient population, include fatigue, headache, diarrhea, abdominal pain, dyspepsia, and weight decrease. There were no important differences in adverse event rates related to dose, gender or race. Adverse events occurred more often in the fixed dosage trials and at higher doses, and less often in the dose-escalation trial, where the dose was increased every four weeks. GI side effects tend

to occur at initiation of treatment and when titrating doses. These symptoms are generally self-limiting and can be managed by encouragement and management of present dose, omitting one or more doses, or by temporarily decreasing dosage.

Pharmacology

Mechanism of Action: Cholinergic loss that occurs in patients with Alzheimer's disease has been correlated with a degree of cognitive impairment and density of amyloid plaques. Galantamine competitively and reversibly inhibits acetylcholinesterase, the enzyme that breaks down acetylcholine, enhancing cholinergic function, which leads to a decrease in cognitive impairment.

Absorption/Distribution: Galantamine is rapidly and completely absorbed with peak concentrations occurring in about an hour. Bioavailability of the tablet and the solution is very similar at about 90%. Administration with food did not effect the AUC of galantamine but C_{max} decreased by 25% and T_{max} was delayed by 1.5 hours. The mean volume of distribution is about 175 L. Galantamine is 18% protein bound at therapeutically relevant concentrations, and mainly distributed to blood cells.

Metabolism/Elimination: Galantamine is metabolized by the hepatic cytochrome P450 enzymes, primarily CYP2D6 and CYP3A4. Ninety five percent of the drug is excreted in the urine, and about five percent excreted in the feces. Twenty percent of the dose is excreted unchanged in the urine with the rest being metabolized to other forms.

Patient Information

1. Do not take galantamine if you are allergic to it or any of the components used in the formulation of the tablet. If you experience an allergic reaction to galantamine, discontinue use and seek emergency medical attention.
2. Galantamine should be taken twice daily with the morning and evening meals. Each dose should be taken with a full glass of water.
3. There are many medications that can interact with galantamine, so talk to your doctor or pharmacist before taking any medication.
4. Galantamine causes gastrointestinal side effects, which should be self-limiting, but dosage adjustment might be needed.

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Penlac® (ciclopirox)

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Introduction

Penlac® [ciclopirox olamine (syé-klo-PEER-ox)] is a new drug formulation that was approved by the FDA in June 2000 for the topical treatment of onychomycosis without lunula involvement that is due to *trichophyton rubrum*. Although its exact mechanism is unknown, ciclopirox is thought to produce its effect by chelating cations which leads to the inhibition of enzymes that are responsible for the breakdown of peroxidases in the fungal cell.

Therapeutic Recommendation

Ciclopirox is the first prescription topical therapy approved for the treatment of onychomycosis. It is a broad-spectrum antifungal agent that inhibits the growth of fungi by inhibiting the breakdown of peroxides within fungal cells. Usage requires significant involvement of both the patient and physician. Ciclopirox therapy requires use for up to 1 year, along with removal of the unattached portion of the infected nail by a health care professional. According to clinical trials, at least 6 months of therapy may be required before beneficial effects become evident. These trials have

also shown that complete resolution of color may not be achieved even with adequate treatment. A pharmacoeconomic analysis comparing the cost of acquisition, medical management, and adverse effects management of ciclopirox topical solution in the treatment of toe onychomycosis versus oral antifungals (terbinafine, itraconazole, fluconazole, and griseofulvin) has shown the cost effectiveness associated with the use of ciclopirox topical solution.

Clinical trials have also shown that ciclopirox topical solution has little systemic absorption and minimal side effects associated with its use. The most common side effects are local rash related events most commonly manifested as erythema. Other side effects may include nail discoloration, change in shape, and irritation. These side effects were transient, decreasing with continuation of treatment. The minimal side effects associated with ciclopirox use give it an advantage over other treatments. Other oral agents commonly used for the treatment of onychomycosis, such as terbinafine (Lamisil®) and itraconazole (Sporanox®), have significant side effects and drug interactions. For example, terbinafine and itraconazole are both associated with a high incidence of gastrointestinal side effects (11%). Terbinafine is contraindicated in patients with renal or hepatic dysfunction and is an inhibitor of CYP2D6 enzymes. Therefore, it is associated with significant drug-drug interactions such as warfarin, SSRIs, and tricyclic antidepressants. Similarly, itraconazole is associated with significant adverse effects such as hepatic dysfunction and is contraindicated in patients with left ventricular dysfunction or CHF. Itraconazole also inhibits CYP3A4 enzymes and is associated with significant drug-drug interactions such as digoxin and phenytoin.

Although it is less expensive and more tolerable, it is important to note that ciclopirox use requires a longer duration of therapy, increased maintenance by both the physician and patient, and has decreased efficacy compared to other agents used in treating onychomycosis. Because of its characteristics, ciclopirox provides an alternative means of ther-

apy for patients who are not eligible for treatment with oral agents; whether it is due to a lack of tolerability, cost, hepatic or renal impairment, potential drug interactions, or oral treatment failure.

Dosing and Administration

Ciclopirox topical solution is available as 8% concentration in bottles of 3.3 ml and 6.6 ml with an applicator brush included. Ciclopirox is applied to the affected nail once daily, as well as to 5 mm of the surrounding skin, the nail bed and the underside of the nail plate. The solution should be applied 8 hours prior to bathing, preferably at bedtime. When reapplying, the new layer should be applied directly over the old layer. Alcohol should be used once a week to remove all the layers of medication, then the reapplication process should continue.

It is recommended that the patient have the unattached, infected part of the nail removed monthly by a healthcare professional, also trimming the nail and filing the excess horny material. It is also recommended that after the ciclopirox is removed weekly, the patient should file and trim the affected nail prior to reapplication.

Cost Comparison

Medication/Dose	Cost*			
	RiteAid	KMart	Kroger	Drug Emporium
Penlac® (ciclopirox) 8% nail lacquer (3.3 ml)	84.98	71.97	78.99	85.20
Sporanox® (itraconazole) 100 mg capsules (200mg qd)	496.98	468.99	532.59	411.67
Lamisil® (terbinafine) 250 mg tablets (250mg qd)	266.99	251.97	287.19	268.32

*Prices represent cost to the patient for a thirty -day supply

Warning/Precautions

For external use only- avoid contact with eyes and mucous membranes. If irritation or sensitivity occurs discontinue treatment.

Contraindications

Ciclopirox should not be used in patients with hypersensitivity to ciclopirox or any of its components.

Special Populations

Insulin Dependent Diabetes Mellitus or Diabetic Neuropathy: There is no clinical data reflecting outcomes when used in persons with diabetes or diabetes-associated neuropathy. The risk versus benefit of a health care professional removing the unattached portion of the infected nail should be weighed prior to prescribing.

Geriatrics: Current clinical trials have not included a large enough population of patients greater than 65 years of age to determine if they respond differently to ciclopirox than the younger population. Based on clinical experience, there has not been a significant variance in response between younger individuals and the elderly.

Pregnancy: Ciclopirox is classified as a pregnancy category B. There are no human trials that show safety and efficacy during pregnancy, but animal studies demonstrate no risk of teratogenicity.

Lactation: It is unknown whether ciclopirox is excreted in breast milk. Therefore, caution should be used when administering to a nursing mother.

Pediatrics: No clinical trials have been performed to determine the safety and efficacy of ciclopirox in the pediatric population.

Drug Interactions

The use of ciclopirox solution concomitantly with oral antifungal agents for treatment of onychomycosis is not recommended. There have been no studies conducted to determine if ciclopirox will alter the effectiveness of these agents.

Adverse Effects:

Ciclopirox is generally well tolerated with few adverse effects. The most frequent adverse events in clinical trials were local skin reactions/rash related events. The most common of these was erythema of the application area including skin near the nail plate ($\leq 10\%$). There were also nail disorders that occurred, such as ingrown toenails, discoloration, shape change and irritation ($\leq 3\%$). There were also application site reactions such as pain, intermittent burning and tingling sensations ($\leq 3\%$). All adverse reactions were mild and diminished throughout the studies without discontinuing treatment.

Pharmacology

Mechanism of Action: Ciclopirox is a broad-spectrum antifungal agent that inhibits the growth of dermatophytes. The exact mechanism of action of ciclopirox is unknown. However, it has been shown to chelate polyvalent cations such as iron or aluminum thereby causing the inhibition of metal-dependent enzymes that lead to the breakdown of peroxides within the fungal cells.

Absorption/Distribution: Ciclopirox topical solution is minimally absorbed into systemic circulation. Clinical trials have shown <5% absorption of the applied dose. Also, after one month of discontinuation, serum and urine levels of ciclopirox were undetectable. Ciclopirox has been shown to penetrate approximately 0.4 mm into the nail surface.

Metabolism/Excretion: The ciclopirox that is absorbed from the topical solution is eliminated through urine and the feces. It is mainly eliminated as unchanged compound or as a glucuronide.

Patient Information

1. Avoid contact with eyes and mouth.
2. Apply to the fingernail and toenail area only
3. Apply sufficient amount of solution with applicator brush to the nail and the surrounding skin as well as underneath the nail.
4. Visit physician at least monthly for the duration of treatment to remove the unattached portion of the infected nail.

5. Do not use any other product on the nail, including cosmetic nail polishes.
6. Avoid applying near an open flame.
7. Apply once daily at least 8 hours before bathing, preferably at bedtime.
8. Apply each daily treatment without removing the application from the day before.
9. Remove medicine with rubbing alcohol once a week.
10. File or trim nail after removing medicine and prior to the next application.
11. May need to use the medicine for up to 6 months before seeing any improvement and a clear nail may not be achieved even with 1 year of treatment.

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