

## More about ACE Inhibitors: Renal Effects and Implications from the HOPE Trial

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Angiotensin-converting-enzyme (ACE) inhibitors are a versatile and increasingly useful class of therapeutic drugs. In addition to their antihypertensive effects, ACE inhibitors have been shown to reduce morbidity and mortality in patients with heart failure,<sup>1-5</sup> and to slow the progression of renal dysfunction in patients with diabetes<sup>6-7</sup> or chronic renal disease.<sup>8</sup> Currently, there are ten ACE inhibitors available in the United States. There are a number of differences among the ACE inhibitors in terms of FDA-approved indications, dosing regimens, and recommended dosing adjustments in patients with renal or hepatic dysfunction (see Table I on page 19). This article will discuss recent changes to the UWMC/HMC formulary concerning ACE inhibitors based on information from the HOPE (Heart Outcomes Prevention Evaluation)<sup>9</sup> trial, ACE inhibitor use in diabetic nephropathy, and ACE inhibitor-associated acute elevation of serum creatinine.

Angiotensin converting enzyme is found in various tissues in the body; its highest production is in endothelial cells in blood vessels. ACE converts relatively inactive angiotensin I to active angiotensin II. Angiotensin II is a potent vasoconstrictor that stimulates aldosterone secretion. ACE inhibitors inhibit the production of angiotensin II, resulting in a vasodilatory effect. They also block the degradation of bradykinin, which results in further vasodilation.<sup>10</sup> In addition to ACE inhibitors' antihypertensive properties, they exhibit anti-inflammatory properties, regulate endothelial function, and delay the development of atherosclerosis.<sup>11</sup>

### Recent changes to the UWMC/HMC formulary concerning ACE inhibitors

The UWMC/HMC formulary includes a number of ACE inhibitors, each with different FDA-approved indications targeted toward various patient populations. At the February UWMC/HMC Pharmacy and Therapeutics (P&T) Committee meeting, a review of all ACE inhibitors was presented and two changes were made to the formulary: benazepril was removed and ramipril was added.<sup>12</sup>

Benazepril was originally added to the formulary largely because it was relatively less expensive when compared to other ACE inhibitors. Last year, enalapril became available as a generic product and provided a significant cost saving to patients. Currently, benazepril ranks as one of the most expensive ACE inhibitors. In view of the fact that its indication is limited to hypertension and because of its high patient cost, the P&T Committee decided to remove benazepril from the formulary.<sup>12</sup> It is recommended that patients who currently receive benazepril as an antihypertensive agent be converted to generic enalapril, which is the only generic ACE inhibitor currently on the formulary. Although the FDA approved generic production of lisinopril in December 2001, the first generic product won't be available for three to four months. The price of this generic product is expected to be slightly less than the brand name product during the first six-month period since the generic manufacturer is authorized to be the sole manufacturer

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**UWMC/HMC Patient Charge for a One-Month Supply of Formulary ACE Inhibitors**

Drug Name & Dose	UWMC Outpatient Charge
Captopril 12.5mg TID 25mg TID 50mg TID	\$5.60 \$5.65 \$8.90
Enalapril 2.5mg BID 5mg Q day 10mg BID 20mg BID	\$12.50 \$8.75 \$14.10 \$18.70
Lisinopril 5mg Q day 10mg Q day 20mg Q day 40mg Q day	\$22.50 \$22.45 \$23.40 \$42.65
Ramipril* 10mg Q day	\$41.15

\*Restricted to patients meeting HOPE trial criteria.

**Ramipril is available on the UWMC/HMC formulary ONLY for patients who meet the HOPE trial criteria.**

during this time. As a result, significant savings from generic lisinopril will not be seen in the next eight to ten months. Because benazepril currently comprises 36% of the total ACE inhibitor utilization and 47% of the cost market share at UWMC, it is vital to recognize the cost saving potential to patients and the institution by using the less expensive product, generic enalapril, which has equivalent efficacy.<sup>12</sup>

In addition, the UWMC/HMC P&T Committee added ramipril, with a target dose of 10mg daily, to the formulary as a therapeutic option for patients who meet the HOPE trial criteria. Candidates for use of ramipril include men and women over the age of 55 without left ventricular dysfunction or heart failure who have: 1) a history of coronary artery disease, stroke, peripheral vascular disease, or 2) diabetes PLUS at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking, or documented microalbuminuria). Of the four ACE inhibitors available on the formulary, ramipril is the most expensive agent, therefore use is restricted to patients meeting the HOPE trial criteria.<sup>12</sup>

**Implications from the HOPE trial**

The HOPE trial examined the benefits of ramipril 10mg once daily compared to placebo in 9,541 high-risk patients over the age of 55 who did not have left ventricular dysfunction or heart failure. A summary of the inclusion criteria, exclusion criteria and results of the HOPE trial is included in Table II of this paper. Although patients with cardiovascular disease (CVD) and/or diabetes were included, 79% of the patients in the study had a history of CVD or peripheral vascular disease.<sup>9</sup> Based on the analysis by Reeder, for every 1,000 patients who were treated with ramipril in the HOPE trial, the projected number of events prevented after four to five years of treatment were as follows: 18 deaths, 16 myocardial infarctions, 26 revascularization procedures, 16 cases of new diabetes, and nine strokes.<sup>13</sup> The number of patients needed to treat for four to five years to prevent one death is 55. Thus ramipril was shown to reduce the rate of death, myocardial infarction, stroke, revascularization procedures, cardiac arrest, heart failure, diabetic complications and new cases of diabetes in a group of high risk patients.

**Table II: Effect of an Angiotensin-Converting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients** (by the Heart Outcomes Prevention Evaluation (HOPE) study investigators)<sup>9</sup>

Purpose	Dose	Inclusion Criteria	Exclusion Criteria	Primary Endpoints (after a mean of 4.5 years follow-up)			Secondary Endpoints		
				Ramipril n=4645	Placebo n=4652	Risk Reduction		Risk Reduction	
Determine the effects of ramipril in patients who were at high risk for cardiovascular events who did not have left ventricular dysfunction or heart failure	Ramipril 10mg q day or placebo; and vitamin E or placebo, according to a two-by-two factorial design	1) Men & Women ≥ 55 years old  2) Patients with history of coronary artery disease, stroke, peripheral vascular disease  3) Patients with diabetes PLUS at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein levels, cigarette smoking, or documented microalbuminuria)	Patients with heart failure, known ejection fraction <40%, those already taking an ACE-Inhibitor or vitamin E, those with uncontrolled hypertension or overt nephropathy, or a recent myocardial infarction or stroke within four weeks before the study began.						
							Revascularization	↓ 15% (p=0.002)	
				<b>Incidence of myocardial infarction</b>	9.9%	12.3%	↓ 20% (p<0.001)	Hospitalization for unstable angina	↓ 2% Not significant
							Hospitalization for heart failure	↓ 12% Not significant	
				<b>Incidence of stroke</b>	3.4%	4.9%	↓ 32% (p<0.001)	Complications related to diabetes	↓ 16% (p=0.03)
							Heart failure	↓ 23% (p<0.001)	
				<b>Death from cardiovascular causes</b>	6.1%	8.1%	↓ 26% (p<0.001)	Cardiac arrest	↓ 38% (p=0.02)
							Worsening angina	↓ 11% (p=0.04)	
			<b>Myocardial infarction, stroke, or death from cardiovascular cause</b>	14%	17.8%	↓ 22% (p<0.001)	New diagnosis of diabetes	↓ 34% (p<0.001)	
						Unstable angina with ECG changes	↓ 3% Not significant		

Table I: Summary of FDA-Approved Indications and Dosing Regimens among ACE Inhibitors<sup>1,4,17</sup>

		FORMULARY AGENTS						NON-FORMULARY AGENTS					
		Captopril (Capoten)	Enalapril (Vasotec)	Lisinopril (Zestril/Prinivil)	Ramipril (Aitace)	Benazepril (Lotensin)	Fosinopril (Monopril)	Moexipril (Univasc)	Perindopril (Aceon)	Quinapril (Accupril)	Trandolapril (Mavik)		
Hypertension	Initial dose	25mg BID or TID	5mg Q day	10mg Q day	2.5mg Q day (Non preferred agent for this indication)	10mg Q day	7.5mg Q day 1 hour prior to meal	4mg Q day	10mg or 20mg Q day	1mg Q day; 2mg Q day for African American patients			
	UWMC outpatient charge (1 month supply)	\$5.60	\$13.45	\$22.50	(Non preferred agent for this indication)	—	—	—	—	—			
	Maintenance dose	50mg BID or TID	10-40mg Q day in 1 or 2 divided doses	20-40mg Q day	2.5-20mg Q day in 1 or 2 divided doses	20-40mg Q day in 1 or 2 divided doses	7.5 - 30mg Q day in 1 or 2 divided doses	4-8mg Q day	20-80mg Q day in 1 or 2 divided doses	2-4mg Q day			
Heart Failure	Initial dose in patients on diuretic	6.25 or 12.5mg BID or TID	2.5mg Q day	5mg Q day	1.25mg Q day	5mg Q day	3.75mg Q day	2-4mg Q day in 1 or 2 divided doses	5mg Q day	0.5mg Q day			
	Initial dose	25mg TID	2.5mg BID	5mg Q day	No indication	No indication	No indication	No indication	5mg BID	1mg Q day			
	UWMC outpatient charge (1 month supply)	\$5.60	\$12.50	\$22.50	—	—	—	—	—	—			
Left ventricular dysfunction post myocardial infarction	Target dose	50mg TID	20mg BID	20mg Q day	No indication	No indication	No indication	No indication	40mg Q day	20mg BID			
	Initial dose	6.25mg x 1 dose, then 12.5mg TID, increase to 25mg TID gradually over several days	2.5mg BID	No indication	2.5mg BID (Non preferred agent for this indication)	No indication	No indication	No indication	No indication	No indication	1mg Q day		
	Target dose	50mg TID	10mg BID	No indication	5mg BID	No indication	No indication	No indication	No indication	No indication	4mg Q day		
Special Indications		Type 1 diabetic nephropathy: 25mg TID	No special indication	Acute myocardial infarction: In hemodynamically stable patients, 5mg x 1 dose within 24 hours of myocardial infarction, 5mg x 1 dose after 24 hours, 10mg x 1 dose after 48 hours, 10mg Q day for 6 weeks	Risk reduction of cardiovascular events (ONLY for patients who meet HOPE trial criteria): 2.5mg Q day x 1 week, 5mg Q day x 3 weeks, 10mg Q day (Ramipril 10mg daily = \$41.15 per month)	No special indication	No special indication	No special indication	No special indication	No special indication	No special indication		
	Maximum total daily dose	Heart failure: 450mg. Other indications: 150mg	40mg	80mg	20mg	80mg	30mg	16mg	80mg	80mg	8mg		
Initial dose in patients with renal dysfunction	CrCl<30mL/minute	75% of dose Q day	2.5mg Q day	5mg Q day	Hypertension: 1.25mg Q day; Maximum: 5mg/day Left ventricular dysfunction post myocardial infarction: 1.25mg Q day; Maximum: 2.5mg BID	5mg Q day	3.75mg Q day Maximum dose: 15mg/day	Safety and efficacy in patients with CrCl<30mL/minute not clearly established	5mg Q day	0.5mg Q day			
	CrCl<10mL/minute	50% of dose Q day	2.5mg Q day	2.5mg Q day Maximum dose: 40mg/day	No information	5mg Q day	No information	Unknown	2.5mg Q day	0.5mg Q day			
	Hemodialysis	25-30% dose after 4 hours of dialysis	2.5mg on dialysis day	2.5mg Q day, Maximum dose: 40mg/day	No information	Give after dialysis	No information	No information	No dose adjustment needed	Insufficient data	Unknown		
Initial dose in patient with hepatic dysfunction											NO DOSING ADJUSTMENT IS REQUIRED.		
Dosage form available		12.5, 25, 50, 100mg tablet	2.5, 5, 10, 20mg tablet	2.5, 5, 10, 20, 40mg tablet	1.25, 2.5, 5, 10mg capsule	5, 10, 20, 40mg tablet	7.5mg, 15mg tablet	2, 4, 8mg tablet	5, 10, 20, 40mg tablet	1, 2, 4mg tablet			

**Captopril, enalapril, lisinopril, and ramipril (for patients who meet the HOPE trial criteria) are currently on the UWMC/HMC formulary. Benazepril has been removed. A dosing conversion ratio of 1:1 is suggested when converting patients from benazepril to enalapril. Patients with congestive heart failure or renal insufficiency may require monitoring of serum creatinine and potassium levels one to two weeks after conversion.**

**Candidates for use of ramipril include: men and women over age 55 without left ventricular dysfunction or heart failure with**

- 1) history of coronary artery disease, stroke, peripheral vascular disease; OR**
- 2) diabetes PLUS at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein levels, cigarette smoking, or documented microalbuminuria).**

**Initiation of ACE inhibitor therapy is recommended for all type 1 diabetic patients with microalbuminuria, including patients without hypertension.**

How to apply the results of the HOPE trial to clinical practice is open to discussion. One school of thought would limit the application of the results of a clinical trial to the specific agent used in that study. On the other hand, practitioners often merge clinical experience with results gleaned from previous clinical trials to make reasonable assumptions, since many aspects of clinical practice cannot, or will not, ever be adequately tested.<sup>18</sup>

A strict interpretation of the HOPE trial results would argue that since ramipril lowered the incidence of myocardial infarction, stroke, and death from cardiovascular events in the study population, and since it is unknown whether other ACE inhibitors would provide similar benefits, then ramipril ought to be prescribed for these high risk patients. Because ramipril is one of the ACE inhibitors that exhibits a high tissue ACE inhibition, it has been argued that ramipril's high tissue binding properties may explain the study findings.<sup>19</sup>

However, another interpretation is also plausible. Since the study compares ramipril to placebo only, and since ACE inhibitors have been shown to have relatively similar efficacy for other indications, (i.e., congestive heart failure, left ventricular dysfunction post myocardial infarction, and diabetic nephropathy<sup>6, 7</sup>), it is reasonable to assume that any ACE inhibitor would show the beneficial results demonstrated in the HOPE trial.<sup>19</sup> Moreover, small differences in efficacy between various ACE inhibitors may not be clinically significant.<sup>20</sup> If this interpretation is accepted, then any ACE inhibitor could be prescribed for patients meeting the HOPE trial criteria.

#### **Use of ACE inhibitors in diabetic nephropathy**

A number of clinical trials have shown that ACE inhibitor therapy with captopril, enalapril, or lisinopril slows progression of diabetic nephropathy.<sup>6, 21, 22</sup> This is one of the long-term complications of diabetes, affecting about 10 - 21% of all patients with diabetes. Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD), and accounts for about 40% of new cases of ESRD.<sup>23</sup> Risk factors for developing diabetic nephropathy include: poor glycemic control, hypertension, glomerular hyperfiltration, or African American, Mexican, or Native American background. Microalbuminuria, defined as urinary albumin excretion  $\geq 30\text{mg}/24$  hours, is an early indicator of diabetic nephropathy.<sup>24</sup>

Blood pressure (BP) control with a goal of  $<125/75$  mmHg, use of ACE inhibitors, glycemic control, and protein restriction are important clinical components in slowing the progression from microalbuminuria to overt nephropathy and subsequently to ESRD.<sup>24, 25</sup> Although the mechanism of action is unclear, ACE inhibitors have been shown to reduce protein excretion by decreasing intraglomerular pressure, and to improve size selective properties of the glomerular capillary wall. Clinical studies have shown that ACE inhibitor therapy delays the progression of diabetic nephropathy in type 1 diabetic patients; however, fewer studies have evaluated the use of ACE inhibitors in type 2 diabetic patients.<sup>26</sup> Recently, angiotensin receptor blockers (ARBs) demonstrated delay in development of nephropathy in patients with type 2 diabetes.<sup>27, 28</sup> Further comparative studies between ARBs and ACE inhibitors are needed to determine whether one group of agents is superior to the other.

Significant reduction in either urinary albumin and/or protein excretion compared to baseline was seen in six out of the seven clinical trials which investigated the use of ACE inhibitors in patients with type 1 or type 2 diabetes (see Table III).<sup>6, 21-22, 29-32</sup> As a result, use of ACE inhibitors is recommended for all type 1 diabetic patients with microalbuminuria, including patients without hypertension. This is

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**In patients with type 2 diabetes, ACE inhibitor therapy is recommended for those with progressive microalbuminuria, albuminuria, or hypertension.**

because a high proportion of patients with type 1 diabetes progress from microalbuminuria to overt nephropathy and subsequently to ESRD. In patients with type 2 diabetes, the rate of progression of microalbuminuria to overt nephropathy and ESRD is less predictable. The use of ACE inhibitors is recommended in those type 2 diabetic patients with progression of microalbuminuria, albuminuria, or those who develop hypertension.<sup>24</sup>

**Table III: Clinical Trials Using ACE Inhibitors in Patients with Diabetic Nephropathy**

Study	N	Treatment	Duration of follow-up (years)	Achieved MAP (mmHg) in ACE inhibitor group	Renal effects observed in the ACE inhibitor group at the end of the study	Other pertinent results seen in the study
<b>Patients with type 1 diabetes were included in the following studies:</b>						
Lewis EJ, et al <sup>6</sup>	207	Captopril 25mg TID vs. placebo	3	97	Incidence of doubling in serum creatinine was significantly less with less proteinuria seen in captopril group vs. placebo	Captopril associated with 50% reduction in the risk of combined end points of death, dialysis, and transplantation
Captopril study <sup>21</sup>	235	Captopril 50mg BID vs. placebo	2	93	Significantly lower risk of progression to clinical albuminuria in captopril group vs. placebo	Placebo group associated with significantly higher albumin excretion rate per year
Parving, et al <sup>22</sup>	32	Captopril 74mg BID (on average) vs. placebo	8	Arterial BP 127/79	Reduction in albuminuria in captopril group vs. increase in albuminuria in control group relative to baseline	Arterial BP significantly lower in captopril group vs. placebo group
<b>Patients with type 2 diabetes were included in the following studies:</b>						
Lebovitz, et al <sup>29</sup>	28	Enalapril 5-40mg Q day vs. placebo	3	96	Reduction in urine albumin or protein excretion in enalapril group vs. placebo	No significant change in serum creatinine compared to baseline in either group
Nielsen, et al <sup>30</sup>	21	Lisinopril 10-20mg Q day vs. atenolol 50-100mg Q day	3	112	Lisinopril associated with significant reduction in albuminuria vs. atenolol group	No significant difference in reduction of GFR between treatment groups
Bakris, et al <sup>31</sup>	18	Lisinopril, atenolol, verapamil SR or diltiazem SR	5	99	Lisinopril associated with significantly slower rate of decline in creatinine clearance vs. atenolol group	Reduction in urinary protein excretion rate in lisinopril group vs. increase in urinary protein excretion rate in atenolol group relative to baseline
HOPE study investigators <sup>32</sup>	35-77	Ramipril 10mg Q day vs. placebo	4.5	Arterial BP 140/76	Significantly fewer of patients developed overt nephropathy in ramipril group vs. placebo	Ramipril associated with significant reduction in risk of a combined microvascular outcome of overt nephropathy, dialysis or laser therapy by 16%

Abbreviations: N = number of patients randomized to an ACE inhibitor in a clinical trial; MAP = mean arterial pressure; BP = blood pressure

**An acute reduction in glomerular capillary pressure and a 20–30% increase in serum creatinine can be seen among patients receiving ACE inhibitor therapy.**

**A stabilization of serum creatinine levels usually occurs within two months after initiation of ACE inhibitor therapy.**

**ACE inhibitor-associated acute elevation of serum creatinine**

Despite the many beneficial effects of ACE inhibitor therapy, one important caution must be noted. Use of ACE inhibitors causes a reduction in blood pressure, glomerular capillary pressure, and glomerular filtration rate (GFR). The inhibition of angiotensin II production causes greater vasodilation in the efferent arteriole of the renal glomerulus than in the afferent arteriole. As a result of these effects, acute reduction of glomerular capillary pressure and a 20% to 30% increase in serum creatinine may be seen.<sup>33,34</sup> This is usually followed by stabilization of serum creatinine levels within the first two months of ACE inhibitor therapy and long-term preservation of renal function.<sup>34</sup>

Acute elevation in serum creatinine associated with ACE inhibitor use usually develops shortly after the initiation of therapy; however, it can develop at any time during ACE inhibitor therapy. There are a number of factors that predispose patients to acute elevation of serum creatinine with ACE inhibitor therapy: renal hypoperfusion due to systemic hypotension, volume depletion from diuretic therapy, bilateral renal artery stenosis, stenosis of a dominant or single kidney, concurrent use of vasoconstrictor agents (e.g. nonsteroidal anti-inflammatory agents (NSAIDs) or cyclosporine), congestive heart failure (CHF) or chronic renal insufficiency of any cause. When one or more of these factors are present in a patient receiving an ACE inhibitor, the decrease in GFR may be greater than 30% compared to baseline.<sup>33,34</sup>

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**If serum creatinine level increases more than 30% after one week of ACE inhibitor therapy, temporary discontinuation of the drug and a thorough investigation for other contributory factors should be instituted.**

**Causes of acute elevation of serum creatinine after the initiation of ACE inhibitor therapy:**

- **Volume depletion (diuretic use)**
- **Vasoconstrictor agents (NSAIDs, cyclosporine)**
- **Inadequate renal perfusion:**
  - poor cardiac output
  - low systemic vascular resistance
- **Presence of renal vascular disease:**
  - bilateral renal artery stenosis
  - afferent arteriolar narrowing (hypertension, cyclosporine)
  - stenosis of dominant or single kidney
  - diffuse atherosclerosis in smaller renal vessels.

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To avoid any renal tubular damage in these patients, serum creatinine and electrolyte levels should be monitored before and one week after initiating ACE inhibitor therapy.<sup>35</sup> If the serum creatinine level increases less than 30%, continue the ACE inhibitor at the same dose and monitor renal function periodically. Discontinuation of the medication or dose reduction should be considered if the serum creatinine level increases more than 30% from baseline. The patient should be evaluated for other factors that could contribute to the increase in serum creatinine. This is particularly important if the serum creatinine level continues to increase more than 30% after discontinuation of the medication.<sup>33,34</sup> In this situation, use of an angiotensin receptor blocker is not a recommended therapeutic alternative because it produces similar renal effects as an ACE inhibitor.<sup>35</sup>

Upon the discontinuation of ACE inhibitor therapy, renal function should be expected to improve within 2–3 days if no renal tubular damage has occurred.<sup>33</sup> Initial or persistent decrease in GFR is reversible despite prolonged ACE inhibitor use.<sup>34</sup> This is because the loss in GFR is caused by a reduction in glomerular capillary pressure, which is returned to baseline when angiotensin II is produced. Reversal of the underlying causes of renal hypoperfusion is key to restoring GFR. Reinitiating the ACE inhibitor could be considered when renal function has been restored. The re-initiation of ACE inhibitor therapy is particularly important in patients with a history of myocardial infarction or CHF, as ACE inhibitor therapy has been shown to lower mortality in these patients. In patients with chronic renal insufficiency, ACE inhibitors should be dosed appropriately (see Table I) or ACE inhibitors that are eliminated both hepatically and renally could be chosen. For patients who receive hemodialysis, an ACE inhibitor that is not removed by dialysis could be considered in order to sustain the level of medication throughout therapy.<sup>34</sup>

The HOPE trial demonstrated the beneficial effects of using an ACE inhibitor in patients at high risk of developing cardiovascular events. Based on current information, it is unclear whether ramipril is the only ACE inhibitor that provides these beneficial effects. The use of ACE inhibitor therapy has been shown to slow the progression of diabetic nephropathy. It is important for practitioners to be aware of the possibility of serum creatinine elevation associated with this class of drugs. In summary, ACE inhibitors have been shown to be helpful for many patients with diabetic nephropathy or cardiovascular disease. Further investigations will provide a clearer understanding of potential benefits of ACE inhibitor therapy.

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## Pharmacy & Therapeutics Committee Actions

Formulary Deletions	Dosage Form(s), Strength(s)	Therapeutic Classification	Use	Comment
Rivastigmine (Exelon)	All dosage forms and strengths	Cholinesterase inhibitor	Treatment of mild to moderate dementia of Alzheimer's disease	Other cholinesterase inhibitors available on the formulary: donepezil (Aricept) and galantamine (Reminyl)
Other Formulary Actions				
Therapeutic Substitution  ONLY for patients with feeding tubes placed or those who cannot take standard proton pump inhibitor oral tablets or capsules	Product		UWMC Formulary Substitution	
	pantoprazole 40mg q day (Intravenous or Oral) OR omeprazole 20mg q day (Non preferred agent)		lansoprazole 30mg q day (Either as the Prevacid Sachet <sup>®</sup> : lansoprazole powder for suspension OR lansoprazole with sodium bicarbonate)	
	pantoprazole 40mg BID (Intravenous or Oral) OR omeprazole 40mg q day OR omeprazole 20mg BID (Non preferred agent)		lansoprazole 30mg BID (Either as the Prevacid Sachet <sup>®</sup> : lansoprazole powder for suspension OR lansoprazole with sodium bicarbonate)	

**2001-2002 "Safety-Related Drug Alerts!" Archives Now Available on UWMC/HMC Drug Information Center PRN Web Site**

Health care providers may now access the 2001-2002 back issues of "Safety-Related Drug Alerts!" from the UWMC/HMC Drug Information Center *PRN* web site (<http://uw.prnrx.org>). Safety-related drug alerts are summaries of drug safety briefings that may be associated with health consequences for patients. Included are briefings regarding prescription and non-prescription drugs, and products regulated as food supplements. Safety-related drug alerts may originate from the FDA, pharmaceutical manufacturers, or other sources deemed reliable. The 2001 archives can be accessed directly from the following URL: <http://depts.washington.edu/druginfo/Alerts/2001.html>; the 2002 archives are available at: <http://depts.washington.edu/druginfo/Alerts/2002.html>.

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