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In This Issue:

- **Tekturna[®]**
- **Apidra[®]**
- **Formulary Update**

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Comprehensive information about
medications, biologics, nutrients,
and drug therapy

Formulary Information

Medication Inservices

Aliskiren (Tekturna[®]) for Hypertension by Kelli Branch, Pharm.D. Candidate

Aliskiren (Tekturna[®]; Novartis Pharmaceuticals) was approved by the Food and Drug Administration (FDA) on March 6, 2007, for the treatment of hypertension, either as monotherapy or in combination with another antihypertensive agent. This is the first approved drug in a new antihypertensive class known as direct renin inhibitors.¹

Hypertension is closely linked to the renin-angiotensin-aldosterone system (RAAS). Decreased blood volume and renal perfusion result in renin secretion from the kidney, which cleaves angiotensinogen to form angiotensin I (Ang I). Angiotensin I is converted to Ang II by angiotensin-converting enzyme (ACE) and other non-ACE pathways. Angiotensin II is a potent vasoconstrictor that increases blood pressure through the release of catecholamines and the provocation of aldosterone secretion and sodium reabsorption. Chronic over-activation of the RAAS contributes to the development of hypertension and end-organ damage. As a direct renin inhibitor, aliskiren blocks the first rate-limiting step of the RAAS cascade, inhibiting renin, and subsequently inhibiting the conversion of angiotensinogen to Ang I.^{2,3}

There are two antihypertensive drug classes that act at later steps of the ACE pathway in the RAAS system.

Angiotensin-converting enzyme inhibitors prevent the production of Ang II and angiotensin II receptor blockers (ARBs) interrupt the binding of Ang II at the receptor without inhibiting the cascade. Both of these classes suppress a negative feedback loop that inhibits renin release and decreases Ang II levels. This leads to a rise in plasma renin concentration (PRC) that results in increased plasma renin activity (PRA). This increased PRA causes an increased formation of Ang I and Ang II, thereby, limiting the antihypertensive benefit of these drugs. Unlike ACE inhibitors and ARBs, aliskiren is able to suppress the renin system at its initiation point, without inducing the reactive rise in PRA.^{2,4,5}

Six randomized, double-blind, placebo-controlled, 8-week clinical trials including approximately 2700 patients with mild-to-moderate hypertension receiving aliskiren were evaluated by the FDA during the approval process. Each study showed a blood pressure reduction when comparing aliskiren to placebo, with optimal responses occurring with aliskiren doses of 150- and 300-mg. The additional reduction from placebo for sitting systolic blood pressure (SBP)/diastolic blood pressure (DBP) ranged from -2.1/-1.7 mmHg (not statistically significant) to -9.3/-5.4 mmHg ($p < 0.05$) in patients

receiving aliskiren 150 mg and $-5.1/-3.7$ mmHg ($p<0.05$) to $-11.2/-7.5$ mmHg ($p<0.05$) in patients receiving aliskiren 300 mg. The most substantial blood pressure lowering occurred within the first 2 weeks of treatment. Patients continued therapy for up to 1 year, with a persistent, decrease in blood pressure. Cessation of treatment resulted in blood pressure gradually returning to baseline over a period of several weeks. There was no evidence of rebound hypertension after abrupt discontinuation of aliskiren. Blood pressure reductions were consistent among all demographic subgroups, although Black patients had smaller reductions, an effect that is also observed in ACE inhibitor and ARB therapy.²

There have also been several 6- to 8-week, randomized trials assessing aliskiren versus or in combination with the following drugs: hydrochlorothiazide (HCTZ), ramipril (Altace[®]), irbesartan (Avapro[®]), valsartan (Diovan[®]), and amlodipine (Norvasc[®]). Villamil and colleagues compared the efficacy of aliskiren alone or in combination with HCTZ in 2776 patients. Reductions in mean sitting DBP (MSDBP) from baseline for aliskiren 150 mg and 300 mg monotherapy were -8.9 ± 0.6 mmHg and -10.3 ± 0.6 mmHg, respectively, whereas for HCTZ 6.25 mg, 12.5 mg, and 25 mg reductions were -9.1 ± 0.6 mmHg, -10.1 ± 0.6 mmHg, and -9.4 ± 0.6 mmHg, respectively. Similar trends were seen in mean sitting SBP (MSSBP) with reductions of -12.2 mmHg and -15.7 mmHg with aliskiren 150 mg and 300 mg, respectively. Mean sitting SBP reductions with HCTZ 6.25 mg, 12.5 mg, and 25 mg were -11 mmHg, -13.9 mmHg, and -14.3 mmHg, respectively (no standard deviations were reported with SBP results). Combination therapy produced even greater reductions from baseline with the maximal effect occurring in patients receiving aliskiren 300 mg and HCTZ 25 mg (MSSBP/MSDBP $-21.2/-14.3$ mmHg, $p<0.05$ vs. monotherapy).⁶

In a study of 837 patients with hypertension and diabetes comparing aliskiren 300 mg, ramipril 10 mg, and the combination of both agents, aliskiren alone reduced DBP 0.6 mmHg more than ramipril alone. The combination of both agents decreased DBP by 1.5 mmHg more than aliskiren alone and 2.1 mmHg more than ramipril alone. The same trends were seen with mean reductions in SBP: 2.7 mmHg more with aliskiren alone vs. ramipril alone, 1.9 mmHg more with combination therapy vs. aliskiren alone, and 4.6 mmHg more with combination therapy vs. ramipril alone. The aliskiren alone and the combination groups had higher responder rates (i.e., mean DBP <90 mmHg and/or a >10 mmHg decrease from baseline) than the ramipril alone group (73.1% vs. 74.1% vs. 65.8%; respectively).⁷

Gradman and colleagues evaluated the efficacy of aliskiren compared to irbesartan in 793 patients. Both aliskiren 150 mg and 300 mg lowered MSSBP/MSDBP similarly to irbesartan 150 mg ($-11.4\pm 1.3/-9.3\pm 0.8$ mmHg, $-15.8\pm 1.2/-11.7\pm 0.8$ mmHg vs. $-12.5\pm 1.2/-8.9\pm 0.7$ mmHg, respectively). Although changes in blood pressure were similar between aliskiren 300 mg and irbesartan 150 mg, a signifi-

cantly greater proportion of patients receiving the higher dose aliskiren achieved blood pressure control (i.e., MSSBP <140 mmHg and MSDBP <90 mmHg).⁸

In another study of 1123 patients, the effects of aliskiren 150 mg and 300 mg monotherapy on blood pressure were compared to valsartan 80 mg, 160 mg, and 320 mg monotherapy. The effects of combination aliskiren and valsartan 150 mg/160 mg and 300 mg/320 mg were also evaluated. Aliskiren monotherapy lowered MSSBP and MSDBP similarly to valsartan with slightly greater reductions occurring with higher doses (MSSBP/MSDBP reductions: aliskiren 150 mg $-12.1\pm 0.95/-10.3\pm 0.62$ mmHg; aliskiren 300 mg $-15\pm 0.96/-10.5\pm 1.07$ mmHg; valsartan 80 mg $-11.2\pm 1.65/-10.5\pm 1.07$ mmHg; valsartan 160 mg $-15.5\pm 1.65/-11\pm 1.07$ mmHg; and valsartan 320 mg $-16.5\pm 1.62/-11.3\pm 1.05$ mmHg). Combination therapy produced an even greater reduction in blood pressure (MSSBP/MSDBP reductions: aliskiren 150 mg/valsartan 160 mg $-16.6\pm 1.62/-12.1\pm 1.05$ mmHg; and aliskiren 300 mg/valsartan 300 mg $-18\pm 1.65/-12.9\pm 1.07$ mmHg).⁹

In a 6-week randomized trial, Munger and colleagues compared the effects of amlodipine 5 mg and 10 mg alone vs. amlodipine 5 mg combined with aliskiren 150 mg. The combination group had a greater reduction in MSDBP (-8.46 mmHg) compared to amlodipine 5 mg alone (-4.84 mmHg) and a similar reduction to amlodipine 10 mg alone (-8.04 mmHg) but with less incidence of edema (2.1% vs. 11.2%). The same trends were seen with reductions in MSSBP (-10.98 mmHg, -4.96 mmHg, and -9.63 mmHg, respectively).¹⁰

Aliskiren has been evaluated for safety in over 6460 patients. Common side effects in these studies included diarrhea (2 to 2.3%; dose-related but noted more frequently in the elderly and women at lower doses) and other gastrointestinal effects such as abdominal pain, dyspepsia, and gastroesophageal reflux. Other adversities occurring at an incidence of $>1\%$ include headache, dizziness, fatigue, back pain, and nasopharyngitis. Two cases of aliskiren-associated angioedema with respiratory symptoms and two cases of periorbital edema without respiratory involvement have been reported. Overall the rate of angioedema with aliskiren is 0.06%. Twenty-six cases of edema involving the face, hands, or body as a whole have been documented in studies; however these rates are similar to those seen with placebo (0.4% vs. 0.5%, respectively). Aliskiren use has also been associated with increased cough (1.1%); however, these rates are only one-third to one-half those of ACE inhibitors. Aliskiren may also cause the following changes in laboratory values: minor increases in blood urea nitrogen or serum creatinine, small increases in serum uric acid (about 6 micromol/L) that is additive when combined with HCTZ (about 40 micromol/L), and rare, but significant increases in creatinine kinase ($>300\%$ normal levels in 1% of patients). Hyperkalemia with aliskiren is rare, but is observed more often when used in combination with an ACE inhibitor. Aliskiren has not been studied in all populations and it is subject to similar precautions and contraindications.

tions as ACE inhibitors and ARBs, including a contraindication in patients that are pregnant or trying to become pregnant. Aliskiren is Pregnancy Category C when used during the first trimester and Category D when used during the second or third trimesters. If pregnancy is detected, aliskiren therapy should be discontinued.² There is no information regarding a possible cross-sensitivity in patients that are allergic to ACE inhibitors or ARBs.¹

Aliskiren is metabolized by the CYP3A4 enzyme, but it does not induce nor inhibit the CYP450 system. It has been found to decrease the maximum concentrations of furosemide (Lasix[®]) by up to 50%.² Irbesartan may reduce maximum aliskiren concentrations by up to 50%; atorvastatin (Lipitor[®]) and ketoconazole (Nizoral[®]) may increase maximum aliskiren concentrations by 50% and 80%, respectively. The exact mechanism by which these agents increase aliskiren levels is unknown; however, it likely involves CYP3A4 inhibition.²

The recommended initial dose of aliskiren is 150 mg once daily, which may be increased to 300 mg daily if additional blood pressure control is needed. Higher doses were evaluated in some clinical trials, but they did not provide a better anti-

hypertensive response, and their use was associated with increased gastrointestinal side effects. Maximal hypertensive effects of a given dose are typically achieved by 2 weeks. Caution should be exercised when using aliskiren in patients with severe renal impairment as this patient population has not been studied. Peak plasma concentrations of aliskiren are reached within 1 to 3 hours. High-fat meals decrease aliskiren's absorption substantially, so it is recommended that patients time their aliskiren dosing around meals. Aliskiren is available as 150 mg and 300 mg tablets.² The average wholesale price for 30 tablets of aliskiren 150 mg is \$71.37 and for 300 mg is \$90.04.¹¹

In clinical trials aliskiren monotherapy is similarly efficacious to several existing antihypertensive agents in reducing blood pressure and is well-tolerated. It may be a likely agent for combination therapy as well, due to its synergistic effects with widely used antihypertensive therapies. A number of outcome studies are currently being conducted and the results of these trials may help clarify the role of aliskiren in therapy. Aliskiren is not on the Cleveland Clinic Formulary of Accepted Drugs.

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Food and Drug Administration (FDA) Takes Action Against Marketed Unapproved Drugs

The Federal Food, Drug, and Cosmetic Act of 1938 required that all new drugs be proven safe in order to be approved by the FDA. It was not until 1962 that the Act was amended so that all new drugs also had to show evidence of efficacy to receive approval. This amendment also required that drugs previously approved as safe between 1938 and 1962 be retrospectively evaluated for efficacy.¹ Even with these mandates, the FDA estimates that there are several hundred prescription drug active ingredients that are unapproved resulting in as many as several thousand drug products that are currently marketed illegally.^{1,2} Many of these are older medications that were developed and marketed prior to the establishment of a formalized approval process. Because these medications did not go through the formal FDA-approval process, they may not meet standards for efficacy, safety, manufacturing quality, or labeling.¹ Some of these unapproved medications may be beneficial, others, however, may pose risks or are unbeneficial; therefore, in June 2006, the FDA made reviewing all marketed drugs to ensure they meet approval criteria a top priority. The FDA began by focusing on those agents with potential safety risks, drugs that lack evidence of effectiveness, and health fraud drugs.¹ This decision has resulted in the recent market removal of several active ingredients and medication products.

In December 2006, the FDA ordered manufacturers to stop marketing unapproved quinine due to serious safety concerns. Although only approved for treating malaria, quinine was often used off-label to prevent and treat nocturnal leg cramps. Since 1969, the FDA has received 665 reports of adverse events associated with quinine use, including 93 deaths. Quinine can cause cardiac arrhythmias including torsade de pointes, QT prolongation, and thrombocytopenia. In addition, it can result in serious drug interactions with medications that inhibit the CYP3A4 isoenzyme (e.g., erythromycin) and some antiarrhythmic agents. Currently, Qualaquin™ 324 mg capsules are the only FDA-approved brand quinine product remaining on the market.³ These capsules are FDA-approved for treating malaria only; product labeling warns against using them for the prevention or treatment of nocturnal leg cramps.⁴

Similar actions have been taken with other unapproved medications. In April 2007, the FDA requested that manufacturing of trimethobenzamide (Tigan®) suppositories used to treat nausea and vomiting cease due to lack of evidence of effectiveness. This decision does not affect the oral or injectable formulations of trimethobenzamide. Other market withdrawals include the antihistamine carbinoxamine because of safety concerns in children under 2 years of age, ergotamine-containing agents used to treat migraines, and time-released drug products containing guaifenesin.⁵ Remaining supplies of many of these unapproved medications were not recalled and are permitted to be dispensed until quantities are exhausted. Some manufacturers of products containing these active ingredients did follow the appropriate approval process and therefore are permitted to continue marketing their individual products.

The FDA's Unapproved Drug Initiative was established to emphasize their commitment to providing consumers with safe and effective medications. However, it will also benefit healthcare providers ensuring that the medications they recommend and prescribe have been thoroughly evaluated. The FDA will continue to assess classes of medications for unapproved products. Each review may differ depending on the agent. For instance, if the removal of an unapproved medication may result in a shortage of a medically necessary agent, the FDA may permit some companies to continue manufacturing while seeking approval.² However, in some cases, medications that have been available for several years, if not decades, may soon become unavailable.

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Insulin Glulisine (Apidra[®]) to be the Sole Rapid-Acting Insulin Analog For Inpatient Use Therapeutic Interchange of Rapid-Acting Insulin Analogs Effective June 27, 2007

- The Cleveland Clinic Pharmacy and Therapeutics (P & T) Committee considers the rapid-acting insulin analogs glulisine (Apidra[®]), aspart (Novolog[®]) and lispro (Humalog[®]) to be therapeutically equivalent
- Insulin glulisine (Apidra[®]) will become the single formulary rapid-acting insulin analog for adult inpatient use at Cleveland Clinic
- Beginning on **Wednesday, June 27, 2007**, a revised insulin order sheet will be distributed for use. The form lists insulin glulisine (Apidra[®]) as the only available rapid-acting insulin
- Beginning Wednesday, June 27, 2007, all new adult inpatient orders written for insulin aspart (Novolog[®]) and insulin lispro (Humalog[®]) will be automatically switched to the same dose of insulin glulisine (Apidra[®]). This is a Cleveland Clinic P & T Committee approved automatic therapeutic interchange
- Inpatients will be switched to insulin glulisine (Apidra[®]) regardless of which rapid-acting analog they are using at home
- Pharmacists will automatically write a therapeutic interchange order for placement in the chart
- This change applies to the adult hospital only. Cleveland Clinic Children's Hospital will still have all rapid-acting analogs available. Outpatients may be prescribed any rapid-acting analog. Novolog[®] Mix and Humalog[®] Mix remain available to inpatients

Contact Jeff Ketz, Pharm.D. (5-7199/2-3539) or the Drug Information Center (4-6456, option #1) with questions.

Insulin Comparison:

	Glulisine (Apidra[®])	Lispro (Humalog[®])	Aspart (Novolog[®])	Regular Human Insulin
Onset	0.2 - 0.5 hours	0.2 - 0.5 hours	0.2 - 0.5 hours	0.5 hours
Duration	3 - 4 hours	3 - 4 hours	3 - 5 hours	6 - 8 hours
Time to peak	0.5 - 1.5 hours	0.5 - 1.5 hours	1 - 3 hours	2 - 4 hours

Formulary Update

The Cleveland Clinic Pharmacy and Therapeutics Committee met on Tuesday, July 10, 2007, and the following decisions were made:

Formulary Additions:

1. **Eculizumab (Soliris[™]):** Eculizumab, a monoclonal antibody, is indicated for the treatment of paroxysmal nocturnal hemoglobinuria to reduce hemolysis. The recommended initial dose is 600 mg administered as a 35 minute intravenous infusion every 7 days for 4 weeks, then 900 mg 7 days later, and then 900 mg every 14 days thereafter. Eculizumab use will be *restricted* to the Department of Hematology and Medical Oncology for outpatient use only.
2. **Temsirolimus (Torisel[™]):** Temsirolimus is a kinase inhibitor that is FDA-approved for the treatment of advanced renal cell carcinoma. The recommended dose is 25 mg once weekly infused over 30-60 minutes. It is recommended to pre-treat patients with diphenhydramine approximately 30 minutes prior to the temsirolimus dose. Concomitant administration of drugs that strongly inhibit or induce the CYP P450 enzyme system should be avoided. Temsirolimus use will be *restricted* to the Department of Hematology and Medical Oncology for outpatient use only.

Formulary Restriction Changes:

1. **Micafungin (Mycamine[®]):** Micafungin will remain *restricted* to the Department of Infectious Diseases. However, recent clinical data have demonstrated equivalent efficacy between 150 mg and 100 mg of micafungin in the treatment of uncomplicated candidemia. The lower dose should be considered in immunocompetent patients with catheter-related candidemias that do not have evidence of endocarditis or osteomyelitis.

2. **Palonosetron (Aloxi[®]):** Palonosetron will remain *restricted* to the Department of Hematology and Medical Oncology for the prevention of chemotherapy-induced nausea and vomiting; however, the restriction will now include inpatients undergoing the Carboplatin Desensitization Protocol as ordered by Gynecologic Oncology Staff Physicians as well as outpatients.

Therapeutic Interchange:

This is a reminder that in the upcoming months all new inpatient orders for levalbuterol (Xopenex[®]) will be automatically therapeutically interchanged with albuterol (Proventil[®]). Patients receiving levalbuterol as an outpatient may be continued on their therapy. Additional information regarding this automatic therapeutic interchange will be communicated in the near future.

Additional Information:

Lactobacillus is classified as a dietary supplement and is not approved by the FDA. According to the Department of Pharmacy's Dietary Supplements Policy (Policy # 03-055), the Department of Pharmacy will not order, stock, or dispense dietary supplements that are not approved for use by the FDA. **Therefore, effective September 5, 2007, Pharmacy will no longer dispense lactobacillus for any indication.**

For more detailed information on the above medications, please consult the Formulary on the Intranet (under Clinical Resources/Drug Information). Furthermore, please call the Drug Information Center at 4-6456, option #1 if there are any questions.

**Cleveland Clinic
Department of Pharmacy/Hb-03
Drug Information Center**