Texas Vendor Drug Program

Drug Use Criteria: Angiotensin-Converting Enzyme Inhibitors

Publication History

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2. Revised **December 2020;** December 2018; December 2016; December 2014; March 2013; April 2011; March 2011; April 2008; June 2003; July 2002; September 2001; June 2001; June 2000; July 1999; June 1998; June 1997.

Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

1.1 Adults

Angiotensin-converting enzyme (ACE) inhibitors are FDA-approved for use in adults for diabetic nephropathy (captopril only), heart failure, hypertension, and improved survival/reduction of complications post myocardial infarction. Combination therapy is FDA-approved for management of hypertension. ACE inhibitors are available as monotherapy as well as combination products with a calcium channel blocker or hydrochlorothiazide. Adult maximum daily doses for ACE inhibitors are summarized in Tables 1 and 2 for mono- and combination therapy, respectively. Dosages exceeding these recommendations will be reviewed.

Table 1. ACE Inhibitors as Monotherapy - Maximum Daily Adult Dose

Drug Name	Treatment Indication	Dosage Form/Strength	Maximum Recommended Dosage
benazepril (Lotensin®, generics)	hypertension	5 mg, 10 mg, 20 mg, 40 mg tablets	80 mg/day*
captopril (generics)	diabetic nephropathy/ proteinuria	12.5 mg, 25 mg, 50 mg, 100 mg tablets	150 mg/day
	heart failure		450 mg/day
	hypertension		450 mg/day
	post myocardial infarction		150 mg/day
enalapril (Vasotec®, generics; Epaned®)	asymptomatic left ventricular dysfunction	2.5 mg, 5 mg, 10 mg, 20 mg tablets; 1 mg/ml oral solution	20 mg/day
	heart failure		40 mg/day
	hypertension		40 mg/day
fosinopril (generics)	heart failure	10 mg, 20 mg (generic only), 40 mg tablets	40 mg/day

Drug Name	Treatment Indication	Dosage Form/Strength	Maximum Recommended Dosage
	hypertension		80 mg/day
lisinopril (Prinivil®, Zestril®, generics; Qbrelis®)	acute myocardial infarction	2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg tablets; 1 mg/ml oral solution	10 mg/day
	heart failure		40 mg/day
	hypertension		80 mg/day
moexipril (generics)	hypertension	7.5 mg, 15 mg tablets	**30 mg/day**
perindopril (Aceon®, generics)	hypertension	2 mg, 4 mg, 8 mg tablets	16 mg/day *elderly, renal function impairment:* 8 mg/day
	myocardial infarction prophylaxis		8 mg/day
quinapril (Accupril®, generics)	heart failure	5 mg, 10 mg, 20 mg, 40 mg tablets	40 mg/day
	hypertension		80 mg/day
ramipril (Altace®, generics)	heart failure (post myocardial infarction)	1.25 mg, 2.5 mg, 5 mg, 10 mg capsules	10 mg/day
	hypertension		20 mg/day
	myocardial infarction/ stroke prophylaxis **in patients 55 years of age or older**		10 mg/day
trandolapril (generics)	hypertension	1 mg, 2 mg, 4 mg tablets	8 mg/day
	post myocardial infarction (heart failure, left ventricular dysfunction)		4 mg/day

[*]Doses as high as 80 mg have provided increased response; however, experience with these higher dosages is limited.

Table 2. Adult Maximum Dosage Recommendations for ACE Inhibitor Combination Therapy in Hypertension Management

Drug Name	Dosage Form/Strength	Maximum Recommended Dosage
amlodipine/benazepril (Lotrel®, generics)	2.5 mg/10 mg, 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 10 mg/20 mg, 10 mg/40 mg capsules	10 mg/40 mg/day
benazepril/ hydrochlorothiazide (Lotensin HCT®, generics)	5 mg/6.25 mg **(generic only),** 10 mg/12.5 mg, 20 mg/12.5 mg, 20 mg/25 mg tablets	20 mg/25 mg/day
captopril/ hydrochlorothiazide (generics)	25 mg/15 mg, 25 mg/25 mg, 50 mg/15 mg, 50 mg/25 mg tablets	150 mg/50 mg/day
enalapril/ hydrochlorothiazide (Vaseretic®, generics)	5 mg/12.5 mg **(generic only),** 10 mg/25 mg tablets	20 mg/50 mg/day
fosinopril/ hydrochlorothiazide (generics)	10 mg/12.5 mg, 20 mg/12.5 mg tablets	80 mg/50 mg/day
lisinopril/ hydrochlorothiazide (Zestoretic®, generics)	10 mg/12.5 mg, 20 mg/12.5 mg, 20 mg/25 mg tablets	80 mg/50 mg/day
moexipril/ hydrochlorothiazide (generics)	7.5 mg/12.5 mg, 15 mg/12.5 mg, 15 mg/25 mg tablets	30 mg/50 mg/day
perindopril/ amlodipine (Prestalia®)	3.5 mg/2.5 mg, 7 mg/5 mg, 14 mg/10 mg tablets	14 mg/10 mg/day
quinapril/ hydrochlorothiazide (Accuretic®, generics)	10 mg/12.5 mg, 20 mg/12.5 mg, 20 mg/25 mg tablets	40 mg/25 mg/day
trandolapril/verapamil (Tarka®, generics)	1 mg/240 mg, 2 mg/180 mg, 2 mg/240 mg, 4 mg/240 mg extended-release tablets	4 mg/240 mg/day

1.2 Pediatrics

Select ACE inhibitors are FDA-approved for use to manage hypertension in pediatric patients. Maximum recommended ACE inhibitor doses for pediatric patients are

summarized in Table 3. Dosages exceeding these recommendations will be reviewed.

Table 3. Pediatric Maximum Recommended Dosages for ACE inhibitors in Hypertension

Drug	Patient Characteristics	Maximum Daily Dosage
benazepril	6 to 17 years of age	0.6 mg/kg/day up to 40 mg/day
enalapril	1 month of age to 17 years of age	**0.58 mg/kg/day** up to 40 mg/day
fosinopril	6 to 17 years of age (> 50 kg)	40 mg daily
lisinopril	6 to 17 years of age	0.6 mg/kg/day up to 40 mg/day

2 Duration of Therapy

There is no basis for limiting ACE inhibitor therapy duration when utilized to manage hypertension, heart failure, and proteinuria associated with diabetic nephropathy, as these conditions require chronic treatment. The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) focused update supports that ACE inhibitor use reduces cardiovascular morbidity and mortality in heart failure patients with reduced ejection fraction. Additionally, the ACC/AHA 2013 guidelines for ST-elevation myocardial infarction (STEMI) recommend immediate ACE inhibitor therapy within the first 24 hours) in patients with an anterior infarction, heart failure, or ejection fraction < 0.40 who have no contraindications for ACE inhibitor use as well, as indefinite therapy with ACE inhibitors post-myocardial infarction for these patients. The ACC/AHA 2014 guidelines for unstable angina/non-STEMI patients recommend immediate ACE inhibitor therapy (within first 24 hours) in those with pulmonary congestion or left ventricular ejection fraction < 0.40, and no hypotension or contraindications to ACE inhibitor therapy. These guidelines also recommend prolonged use of ACE inhibitors in patients with heart failure, left ventricular ejection fraction < 0.40, hypertension, or diabetes mellitus without contraindications to ACE inhibitor therapy to reduce cardiovascular mortality.

3 Duplicative Therapy

The use of two or more ACE inhibitors concurrently is not justified. Additional therapeutic benefit is not realized when ACE inhibitors are used in combination. Patient profiles documenting the receipt of multiple ACE inhibitors will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for ARBs are summarized in Table 4. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

Table 4. ACE Inhibitor Drug-Drug Interactions

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
ACE inhibitors	aliskiren	potential for additive hypotensive effects; increased hyperkalemia risk with this drug combination as both decrease serum aldosterone levels	administer drug combination cautiously; monitor serum potassium levels closely	moderate (DrugReax) 3-moderate (CP)
ACE inhibitors	angiotensin II receptor blockers	potential for enhanced pharmacologic/ adverse effects (e.g., hypotension, hyperkalemia, changes in renal function) as both agents block renin-angiotensin-aldosterone system	avoid combination; if concurrent therapy necessary, monitor blood pressure, potassium and renal function and observe for adverse events	major (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
ACE inhibitors	antidiabetic agents	potential for enhanced hypoglycemic effects due to improved insulin sensitivity by ACE inhibitors	closely monitor blood glucose levels; reduced antidiabetic doses may be necessary	moderate (DrugReax) 3-moderate (CP)
ACE inhibitors	azathioprine	increased risk of anemia, leukopenia with drug combination; mechanism unknown	avoid combination, if possible; if combined therapy necessary, monitor for myelosuppression	major (DrugReax) 2-major (CP)
lisinopril	clozapine	potential for increased serum clozapine levels and enhanced pharmacologic, adverse effects; lisinopril may decrease clozapine renal elimination through unknown mechanism	assess clinical response, monitor serum clozapine levels if drug combination utilized	3-moderate (CP)
ACE inhibitors	cyclosporine	increased risk of acute renal failure, hyperkalemia with drug combination due to ACE inhibition, which causes decreased angiotensin II and aldosterone	closely monitor renal function and serum potassium levels	moderate (DrugReax) 3-moderate (CP)
ACE inhibitors	entecavir	potential for increased entecavir serum levels and enhanced pharmacologic/ adverse effects due to ACE inhibitor effects on renal function	monitor for increased adverse events if drug combination is administered	3-moderate (CP)
ACE inhibitors	eplerenone	increased risk of hyperkalemia as both agents decrease aldosterone levels	closely monitor serum potassium levels	2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
ACE inhibitors	lithium	potential for increased serum lithium levels and enhanced pharmacologic, toxic effects, possibly due to decreased lithium clearance	avoid combination, if possible; if drug combination necessary, monitor serum lithium levels and observe for signs of lithium toxicity	moderate (DrugReax) 3-moderate (CP)
ACE inhibitors	monoamine oxidase inhibitors	potential for additive hypotensive effects	monitor blood pressure closely, if drug combination utilized	3-moderate (CP)
ACE inhibitors	NSAIDs, salicylates, COX-2 inhibitors	potential for decreased antihypertensive effects, increased renal impairment risk (especially in patents dependent on renal prostaglandins for perfusion), with combined therapy due to inhibition of prostaglandin synthesis	monitor blood pressure, renal function, and clinical status if drug combination utilized; low-dose aspirin less likely to reduce ACE inhibitor antihypertensive, cardioprotective effects	moderate (DrugReax) 3-moderate (CP)
ACE inhibitors	potassium-sparing diuretics, potassium salts	ACE inhibitors reduce aldosterone concentrations, resulting in increased potassium concentrations; increased hyperkalemia risk with drug combination due to additive pharmacologic effects	monitor serum potassium levels and signs/symptoms of hyperkalemia if drug combination administered; patients with renal failure, diabetes, advanced age may be at increased risk; use combination cautiously in heart failure patients	major (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
ACE inhibitors	pregabalin	combined therapy may increase risk of developing life-threatening angioedema with respiratory compromise	observe patients closely if drug combination utilized	2-major (CP)
ACE inhibitors	sacubitril/ valsartan (Entresto®)	concurrent administration may result in angioedema due to inhibition of bradykinin degradation	avoid drug combination; monitor blood pressure, renal function, and electrolytes if combined therapy is utilized	contraindicated (DrugReax) 1-contraindicated (CP)
ACE inhibitors	trimethoprim	co-administration may increase risk of additive hyperkalemia due to decreased aldosterone synthesis by ACE inhibitor and potassium-sparing effect on distal nephron by trimethoprim	monitor serum potassium levels and monitor patients for signs/symptoms of hyperkalemia if drug combination administered	moderate (DrugReax) 2-major (CP)
trandolapril/ verapamil	flibanserin (Addyi®)	verapamil (CYP3A4 inhibitor) and flibanserin (CYP3A4 substrate) administered concurrently may result in increased serum flibanserin levels with resultant severe hypotension, syncope, sedation	avoid combined use; if adjunctive use necessary, discontinue CYP3A4 inhibitor for at least 2 weeks before initiating/reinitiating flibanserin therapy, or discontinue flibanserin at least 2 days before starting/restarting CYP3A4 inhibitor therapy	contraindicated (DrugReax) 1-severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
trandolapril/ verapamil	colchicine	colchicine is p-glycoprotein (P-gp) and CYP3A4 substrate; adjunctive use may result in increased colchicine serum concentrations and enhanced pharmacologic/ adverse effects due to P-gp and CYP3A4 inhibition by verapamil	avoid concurrent use; if combined use necessary, observe for serious colchicine adverse effects, including neuromuscular toxicity, and adjust colchicine dosages	contraindicated (DrugReax) 2-major (CP)
trandolapril/ verapamil	dofetilide (Tikosyn®)	concomitant administration may result in increased cardiotoxicity risk (e.g., torsades de pointes, QT interval prolongation, cardiac arrest) due to increased dofetilide absorption/serum levels	combined use is contraindicated	contraindicated (DrugReax) 1-severe (CP)

[*]*Clinical Pharmacology*

5 References

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