Texas Vendor Drug Program

Drug Use Criteria: Angiotensin II Receptor Blockers

Publication History

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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 II receptor blockers (ARBs) as monotherapy are FDA-approved for use in hypertension (all available ARBs), diabetic nephropathy (irbesartan, losartan), heart failure (candesartan, valsartan), stroke prophylaxis (losartan), cardiovascular risk reduction in patients unable to take angiotensin-converting enzyme (ACE) inhibitors (telmisartan), and post-myocardial infarction (valsartan). ARB combination therapy is FDA-approved for use in hypertension [all available ARB combinations, including the newer combination, nebivolol/valsartan (Byvalson®)] and stroke risk reduction in hypertensive patients as well as patients with left ventricular hypertrophy (Hyzaar®). Sacubitril/valsartan (Entresto®) combination therapy is FDA-approved to reduce the risk of cardiovascular death and hospitalization in chronic heart failure with reduced ejection fraction. The maximum recommended daily doses assigned to ARBs as monotherapy and combination therapy for adult patients are summarized in Tables 1 and 2. Patient profiles containing ARB dosage regimens exceeding these recommendations will be reviewed.

Table 1: Maximum Daily Adult Dosages for Angiotensin II Receptor Blockers - Monotherapy

Drug Name	Treatment Indication	Dosage Form/Strength	Maximum Recommended Dosage
azilsartan (Edarbi™)	hypertension	40 mg, 80 mg tablets	80 mg/day
candesartan (Atacand®, generics)	heart failure	4 mg, 8 mg, 16 mg, 32 mg tablets	32 mg/day
	hypertension		32 mg/day
eprosartan (generics)	hypertension	600 mg tablets	800 mg/day

Drug Name	Treatment Indication	Dosage Form / Strength	Maximum Recommended Dosage
irbesartan (Avapro®, generics)	diabetic nephropathy	75 mg, 150 mg, 300 mg tablets	300 mg/day
	hypertension		300 mg/day
losartan (Cozaar®, generics)	diabetic nephropathy	25 mg, 50 mg, 100 mg tablets	100 mg/day
	hypertension		100 mg/day
	hypertension with left ventricular hypertrophy/ stroke prevention		100 mg/day
olmesartan (Benicar®, generics)	hypertension	5 mg, 20 mg, 40 mg tablets	40 mg/day
telmisartan (Micardis®, generics)	**cardiovascular risk reduction/** stroke prevention/ myocardial infarction prevention	20 mg, 40 mg, 80 mg tablets	80 mg/day
	hypertension		80 mg/day
valsartan (Diovan®, generics)	heart failure	40 mg, 80 mg, 160 mg, 320 mg tablets	320 mg/day in divided doses
	hypertension		320 mg/day
	left ventricular dysfunction/failure after myocardial infarction		320 mg/day in divided doses

Table 2: Maximum Daily Adult Dosages for Angiotensin II Receptor Blockers - Combination Therapy

Drug Name	Treatment Indication	Dosage Form / Strength	Maximum Recommended Dosage
amlodipine/ olmesartan (Azor®, generics)	hypertension	5 mg/20 mg, 10 mg/20 mg, 5 mg/40 mg, 10 mg/40 mg tablets	10 mg/40 mg/day
amlodipine/ valsartan (Exforge®, generics)	hypertension	5 mg/160 mg, 5 mg/320 mg, 10 mg/160 mg, 10 mg/320 mg tablets	10 mg/320 mg/day
amlodipine/ valsartan/ hydrochlorothiazide (Exforge® HCT, generics)	hypertension	5 mg/160 mg/12.5 mg, 10 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/25 mg, 10 mg/320 mg/25 mg tablets	10 mg/320 mg/25 mg/day
azilsartan/ chlorthalidone (Edarbyclor®)	hypertension	40 mg/12.5 mg, 40 mg/25 mg tablets	40 mg/25 mg/day
candesartan/ hydrochlorothiazide (Atacand HCT®, generic)	hypertension	16 mg/12.5 mg, 32 mg/12.5 mg, 32 mg/25 mg tablets	32 mg/25 mg/day
irbesartan/ hydrochlorothiazide (Avalide®, generic)	hypertension	150 mg/12.5 mg, 300 mg/12.5 mg tablets	300 mg/25 mg/day
losartan/ hydrochlorothiazide (Hyzaar®, generic)	hypertension	50 mg/12.5 mg, 100 mg/12.5 mg, 100 mg/25 mg tablets	100 mg/25 mg/day
	stroke reduction in hypertension with left ventricular hypertrophy		100 mg/25 mg/day
nebivolol/ valsartan (Byvalson®)	hypertension	5 mg/80 mg tablets	5 mg/80 mg/day

Drug Name	Treatment Indication	Dosage Form / Strength	Maximum Recommended Dosage
olmesartan/ amlodipine/ hydrochlorothiazide (Tribenzor®, generics)	hypertension	20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/12.5 mg, 40 mg/10 mg/25 mg tablets	40 mg/10 mg/25 mg/day
olmesartan/ hydrochlorothiazide (Benicar HCT®, generics)	hypertension	20 mg/12.5 mg, 40 mg/12.5 mg, 40 mg/25 mg tablets	40 mg/25 mg/day
sacubitril/ valsartan (Entresto®)	heart failure	24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg tablets	**194 mg/206 mg/day** in two divided doses
telmisartan/ amlodipine (Twynsta®, generics)	hypertension	40 mg/5 mg, 40 mg/10 mg, 80 mg/5mg, 80 mg/10 mg tablets	80 mg/10 mg/day
telmisartan/ hydrochlorothiazide (Micardis HCT®, generics)	hypertension	40 mg/12.5 mg, 80 mg/12.5 mg, 80 mg/25 mg tablets	160 mg/25 mg/day
valsartan/ hydrochlorothiazide (Diovan HCT®, generic)	hypertension	80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, 320 mg/ 25 mg tablets	320 mg/25 mg/day

1.2 Pediatrics

Candesartan has recently been FDA-approved to manage hypertension in children 1 to less than 17 years of age. Losartan, olmesartan, and valsartan are FDA-approved to manage hypertension in pediatric patients 6 years of age and older. Irbesartan is not FDA-approved for use in pediatric patients and has not demonstrated sustained efficacy in managing elevated blood pressure in patients 6 years of age and older. Recommended dosages are summarized in Table 3. Dosages exceeding these recommendations will be reviewed.

Table 3: Pediatric Maximum Daily Dosages

Drug	Patient Characteristics	Maximum Daily Dosage
Candesartan	1 to less than 6 years of age	0.4 mg/kg/day
Candesartan	6 to less than 17 years of age: • Less than 50 kg • Greater than 50 kg	• 16 mg/day • 32 mg/day
Losartan	6 years and older	1.4 mg/kg/day to a maximum of 100 mg/day

Olmesartan	• 6 to 16 years of age
	  ▸ Less than 35 kg
	  ▸ Greater than or equal to 35 kg
	• 17 years of age
		• 6 to 16 years of age
		  ▸ 20 mg/day
		  ▸ 40 mg/day
		• 17 years of age
		  ▸ 40 mg/day

Valsartan	• 6 to 16 years of age • 17 years of age	• 2.7 mg/kg/day to a maximum of 160 mg/day • 320 mg/day

- * Irbesartan (off-label) for patients 6 to 16 years of age in doses up to 4.5 mg/kg/day did not effectively lower blood pressure

The safety and efficacy of azilsartan, eprosartan, and telmisartan in pediatric patients have not been established. The safety and efficacy of ARBs in combination with hydrochlorothiazide, aliskiren, or amlodipine in pediatric patients have not been established. Nebivolol/valsartan and sacubitril/valsartan combination therapy is not recommended for use in pediatric patients as safety and efficacy have not been established in this patient population.

2 Duration of Therapy

There is no basis for limiting therapy duration for ARBs as reduction of cardiovascular mortality post-myocardial infarction, stroke risk reduction, managing hypertension, treating diabetic nephropathy, and managing heart failure requires chronic treatment.

3 Duplicative Therapy

Administration of two or more ARBs concurrently is not justified. Additional therapeutic benefit is not appreciated when multiple ARBs are utilized concomitantly. Patient profiles containing regimens comprised of two or more ARBs administered concurrently will be reviewed.

Recent studies have documented concurrent administration of ARBs and ACE inhibitors may result in an increased incidence of adverse effects (e.g., hypotension, hyperkalemia, syncope, renal failure) in patients with heart failure due to myocardial infarction or left ventricular dysfunction, as well as other patients at high risk for vascular events (e.g., diabetic patients) without added benefit. Additional studies have not documented significant benefit with ACE inhibitor-ARB combination therapy in managing hypertension or diabetic nephropathy. The American College of Cardiology/American Heart Association guidelines state that ARB-ACE inhibitor combination therapy may be considered in heart failure patients, not recently post myocardial infarction, who have not responded to target doses of an ACE inhibitor and beta blocker. Adjunctive administration of ARBs and ACE inhibitors should be considered cautiously, if at all, in these patient populations.

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: ARB Drug-Drug Interactions

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
ARBs, nebivolol/ valsartan, sacubitril/ valsartan	aliskiren	increased risk for renal impairment, hyperkalemia, and hypotension with adjunctive administration most likely due to additive effects; documented in ALTITUDE trial (type 2 diabetics with renal impairment had increased stroke, renal complications, hypotension when given ARBs and aliskiren concurrently)	combined administration in diabetics contraindicated by manufacturer; avoid combination in patients with CrCl less than greater than or equal to 60 ml/min; use cautiously together in other patients and closely monitor renal function, serum potassium levels	contraindicated (DrugReax) 2-major (CP)
ARBs, nebivolol/ valsartan, sacubitril/ valsartan	lithium	potential for enhanced lithium pharmacologic /adverse effects with combined administration ; speculated that ARBs augment lithium reabsorption by decreasing lithium renal excretion	monitor patients for increased signs/symptoms of lithium toxicity and adjust lithium doses as necessary; may select alternate cardiovascular therapy that does not interact with lithium	major (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
ARBs, nebivolol/ valsartan, sacubitril/ valsartan	nonsteroidal anti-inflammatory drugs	combined administration may increase risk for renal function deterioration and alter response to antihypertensives, especially in volume-depleted, elderly, or renally compromised patients, due to vasodilatory prostaglandin inhibition	monitor renal function, antihypertensive efficacy when combined administration required	moderate (DrugReax) 3-moderate (CP)
ARBs, nebivolol/ valsartan, sacubitril/ valsartan	potassium-sparing diuretics (e.g., amiloride, spironolactone, triamterene), potassium supplements	combined therapy may increase risk for hyperkalemia as ARBs reduce circulating aldosterone concentrations, resulting in potassium retention; elderly as well as patients with impaired renal function, diabetes, or high potassium diets may be at greater risk	measure serum potassium concentrations, monitor for signs and symptoms of hyperkalemia when administered concurrently, especially in patients with predisposing factors	moderate (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
nebivolol/ valsartan	CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine)	adjunctive administration may result in enhanced nebivolol pharmacologic effects (e.g., reduced heart rate, hypotension) due to increased nebivolol serum levels as nebivolol is metabolized by CYP2D6	combined use should be avoided; if concurrent administration necessary, monitor patients for unwanted pharmacologic/ adverse effects; adjust dosages as needed	major (DrugReax) 2-major (CP)
nebivolol/ valsartan	hypotensive agents	concurrent administration may result in large reductions in sympathetic activity due to added beta-blocking activity; patients may have increased orthostasis and bradycardia	avoid nebivolol use with other beta blockers; withdraw nebivolol slowly over several days in patients prescribed clonidine concurrently	2-major, 3-moderate (CP)
nebivolol/ valsartan	digitalis glycosides	co-administration may increase bradycardia risk as both nebivolol and digitalis glycosides reduce atrioventricular conduction and decrease heart rate	administer nebivolol with digitalis glycosides cautiously and monitor heart rate	moderate (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
nebivolol/ valsartan	calcium channel blockers	combined use of beta blockers like nebivolol with calcium channel blockers can be useful in some circumstances ; however, combined administration may result in additive negative inotropic and/or chronotropic effects	if combined therapy needed, monitor heart rate and cardiac conduction; adjust doses as necessary	moderate (DrugReax) 3-moderate (CP)

- * = Clinical Pharmacology

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