Texas Vendor Drug Program

Drug Use Criteria: Angiotensin II Receptor Blockers

Publication History

1. Developed August 1996.
2. Revised **January 2023;** January 2021; December 2018; December 2016; October 2014; December 2012; March 2011; April 2008; July 2003; July 2002; September 2001; September 2000; July 1999; June 1998; July 1997; December 1996.

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).[1-10] **Losartan/hydrochlorothiazide (Hyzaar®)** is FDA-approved for use in hypertension and stroke risk reduction in **patients with hypertension** as well as patients with left ventricular hypertrophy.[1,2,11] 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.[1,2,12] 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[1-10]

Drug Name	Dosage Form/Strength	Treatment Indication	Maximum Recommended Dosage
azilsartan (Edarbi®)	40 mg, 80 mg tablets	hypertension	80 mg/day
candesartan (Atacand®, generics)	4 mg, 8 mg, 16 mg, 32 mg tablets	heart failure	32 mg/day
		hypertension	32 mg/day
irbesartan (Avapro®, generics)	75 mg, 150 mg, 300 mg tablets	diabetic nephropathy	300 mg/day
		hypertension	300 mg/day

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

Valsartan oral solution is not therapeutically equivalent to the tablet formulation and not substitutable on a mg-per-mg basis

Table 2. Maximum Daily Adult Dosages for Angiotensin II Receptor Blockers - Combination Therapy[1,2,11-23]

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

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

1.2 Pediatrics

Candesartan is FDA-approved to manage hypertension in children 1 to < 17 years of age.[1,2,4] **In 2021, the FDA expanded approval of valsartan to include patients 1 to 5 years of age for treatment of hypertension.**[1,2,9] Losartan, olmesartan, **and valsartan oral solution** are FDA-approved to manage hypertension in pediatric patients 6 years of age and older.[1,2,6,7,10] 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.[1,2,5] **Sacubitril/valsartan is FDA-approved to treat symptomatic heart failure with left ventricular systolic dysfunction in children 1 year and older.**[1,2,12] Recommended dosages are summarized in Table 3. Dosages exceeding these recommendations will be reviewed.

Table 3. Pediatric Maximum Daily Angiotensin II Receptor Blocker Dosages for Hypertension – Monotherapy[1,2,4,6,7,9,10]

Drug	Patient Characteristics	Maximum Daily Dosage
candesartan	*1 to < 6 years of age:* *6 to < 17 years of age:* < 50 kg: > 50 kg:	0.4 mg/kg/day 16 mg/day 32 mg/day
losartan	*6 to 17 years of age:*	1.4 mg/kg/day to a maximum of 100 mg/day
olmesartan	*6 to 16 years of age:* **20 to < 35 kg:** ≥ 35 kg: *17 years of age:*	 20 mg/day 40 mg/day 40 mg/day
valsartan **(oral tablet)**	***1 to 16 years of age:*** *17 years of age:*	**4mg/kg/day to a maximum of 160mg/day** 320 mg/day
valsartan (oral solution)	***6 to 16 years of age:*** ***17 years of age:***	**2.7 mg/kg/day in two divided doses to a maximum of 160 mg/day** **320mg/day**

Table 4. Pediatric Maximum Daily Angiotensin II Receptor Blocker Dosages for Heart Failure – Combination Therapy[1,2,12]

Drug	Patient Characteristics	Maximum Daily Dosage
sacubitril/ valsartan (Entresto®)	***1 to 17 years of age:*** ***<40 kg:*** ***40 to 49 kg:*** ***≥ 50 kg:***	 **6.2mg/kg/day in two divided doses** **144/156 mg/day in two divided doses**

Drug	Patient Characteristics	Maximum Daily Dosage
		194/206 mg/day in two divided doses

The safety and efficacy of azilsartan and telmisartan in pediatric patients have not been established.[1-3,8] The safety and efficacy of ARBs in combination with hydrochlorothiazide, aliskiren, or amlodipine in pediatric patients have not been established.

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.

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.[24-28] 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 5. ARB Drug-Drug Interactions[1-23]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
ARBs, 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 < 60 ml/min; use cautiously together in other patients and closely monitor renal function, serum potassium levels	contraindicated (DrugRex) 2-major (CP)
ARBs, 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 (DrugRex) 3-moderate (CP)
ARBs, 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 (DrugRex) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
ARBs, 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 (DrugRea x) 2-major (CP)

[#]*Clinical Pharmacology*

5 References

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