Therapeutic Class Overview
Cardiovascular, Angiotensin II Receptor Blockers (ARBs) – Combination Products

SCOPE OF REVIEW

- According to the American Heart Association Heart Disease and Stroke Statistics 2016 update the death rates attributable to cardiovascular disease and stroke in 2013 were 223.9 per 100,000 and 36.2 per 100,000, respectively (Mozaffarian et al, 2016).
- Hypertension is an independent risk factor for cardiovascular disease and increases the mortality risks of cardiovascular disease and other diseases (Go et al, 2014).
- An estimated 80 million Americans have high blood pressure (BP). Hypertension is an independent risk factor for cardiovascular disease and increases the mortality risks of cardiovascular disease and other diseases (Mozaffarian et al, 2016).
- Left ventricular (LV) hypertrophy is the enlargement of the ventricle muscle tissue. Often LV hypertrophy develops due to high blood pressure, which requires the ventricle to increase the workload, resulting in thickening of the chamber walls. LV hypertrophy often progresses to heart failure (HF) (Lorell et al, 2000).
- Lowering of blood pressure has been shown to reduce the risk of fatal and nonfatal cardiovascular events including stroke and myocardial infarctions (MI). Improving cardiovascular health and reducing cardiovascular risk also includes lipid control, diabetes management, smoking cessation, exercise, weight management, and limited sodium intake (Go et al, 2014).
- Numerous classes of antihypertensives are available to reduce blood pressure. Some examples of antihypertensives include diuretics, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), beta blockers, and calcium channel blockers (CCBs). Selection of an antihypertensive for a specific patient is determined by patient characteristics such as ethnic group, and the presence of compelling indications such as HF, diabetes (DM), chronic kidney disease (CKD), prevention of recurrent stroke, post-MI, and patients with high risk for coronary heart disease (CHD). Some patients require two or more antihypertensives from different pharmacological classes to achieve blood pressure control (Go et al, 2014; James et al, 2013; Weber et al, 2014). Blood pressure goals for older patients have been a point of debate. The recent SPRINT trial followed patients ≥ 50 years with high blood pressure and increased cardiovascular risks under intense-hypertensive treatment (with a goal of 120 mmHg) compared to standard hypertensive treatment (with a goal of 140 mmHg) over the period of 3.2 years. The trial did end early; however, results demonstrated a reduced primary composite of MI, acute coronary syndrome (ACS), stroke, HF, or cardiovascular death driven mainly by reduced HF events and cardiovascular death with intense-treatment compared to standard treatment (goal 140 mmHg). SPRINT has pointed to potential clinical benefits associated with a more intensive treatment in certain patients (SPRINT Research Group, 2015).
- This review will focus on the combination of ARB with a beta blocker, calcium channel blocker and/or diuretic or both components for the management of hypertension. The ARB combination products are Food and Drug Administration (FDA) approved for the treatment of hypertension. Losartan/hydrochlorothiazide (HCTZ) carries the additional indication of reduction in the risk of stroke in patients with hypertension and LV hypertrophy. The products available in this class include various combinations of an ARB with a beta blocker (nebivolol), calcium channel blocker (amlodipine), a diuretic (HCTZ or chlorthalidone), or both. TEVETEN HCT is no longer available.
- Medispan class: Antihypertensive Combinations. Three subcategories include ARB/CCB combinations, Beta blocker/ARB combination, ARB/Thiazide and Thiazide-like combinations, and ARB/CCB/Thiazide combinations.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ARB/Diuretic Combinations			
ATACAND HCT® (candesartan/hydrochlorothiazide)	various	09/05/2000	✔
AVALIDE® (irbesartan/hydrochlorothiazide)*	various	09/30/1997	✔
BENICAR HCT® (olmesartan/hydrochlorothiazide)	various	06/05/2003	✔
DIOVAN HCT® (valsartan/hydrochlorothiazide)†	various	03/06/1998	✔
EDARBYCLOR® (azilsartan/chlorthalidone)	Takeda Pharmaceutical	12/20/2011	-
HYZAAR® (losartan/hydrochlorothiazide)	various	04/28/1995	✔
MICARDIS HCT® (telmisartan/hydrochlorothiazide)	various	11/17/2000	✔
ARB/Beta Blocker Combination			
BYVALSON® (valsartan/nebivolol)	Allergan/Forest Laboratories	06/03/2016	-
ARB/CCB Combinations			
AZOR® (olmesartan/amlodipine)	various	09/26/2007	✔
EXFORGE® (valsartan/amlodipine)	various	06/20/2007	✔
TWYNSTA® (telmisartan/amlodipine)	various	10/16/2009	✔
ARB/CCB/Diuretic Combinations			
EXFORGE® HCT (valsartan/amlodipine/ hydrochlorothiazide)	various	04/30/2009	✔
TRIBENZOR® (olmesartan/amlodipine/ hydrochlorothiazide)	various	07/23/2010	✔

*As of November 2016, Mylan has made a business decision to discontinue the manufacturing of this generic drug. Other generic products are available for this drug.
†As of February 2016, Sandoz to discontinued the manufacturing of film-coated tables for this generic drug. Other generic products are available for this drug.

(Drugs@FDA, 2016; FDA Drug Shortages, 2016; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2016)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Hypertension	Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy
ARB/Diuretic Combinations		
ATACAND HCT (candesartan/hydrochlorothiazide)	✔ *	-
AVALIDE (irbesartan/hydrochlorothiazide)	✔ †	-
BENICAR HCT (olmesartan/hydrochlorothiazide)	✔ *	-
DIOVAN HCT (valsartan/hydrochlorothiazide)	✔ †	-
EDARBYCLOR (azilsartan/chlorthalidone)	✔ †	-
HYZAAR (losartan/hydrochlorothiazide)	✔ ‡	✔ §
MICARDIS HCT (telmisartan/hydrochlorothiazide)	✔ *	-

ARB/Beta Blocker Combination		
BYVALSON (valsartan/nebivolol)	✔ †	-
ARB/CCB Combinations		
AZOR (olmesartan/amlodipine)	✔ †	-
EXFORGE (valsartan/amlodipine)	✔ †	-
TWYNSTA (telmisartan/amlodipine)	✔ †	-
ARB/CCB/Diuretic Combinations		
EXFORGE HCT (valsartan/amlodipine/ hydrochlorothiazide)	✔ *	-
TRIBENZOR (olmesartan/amlodipine/ hydrochlorothiazide)	✔ *	-

*This fixed-dose combination is not indicated for initial therapy.
†Indicated to treat hypertension in patients not adequately controlled on monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
‡The fixed-dose combination is not indicated for initial therapy, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risks of initiating combination therapy in these patients.
§There is evidence that this benefit does not extend to African American patients.

(Prescribing information: ATACAND HCT, 2016; AVALIDE, 2016; AZOR, 2016; BENICAR HCT, 2016; BYVALSON, 2016; DIOVAN HCT, 2015; EDARBYCLOR, 2016; EXFORGE, 2015; EXFORGE HCT, 2015; HYZAAR, 2015; MICARDIS HCT, 2016; TRIBENZOR, 2016; TWYNSTA, 2016)

- Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials assessing the combination angiotensin II receptor blockers (ARBs) in the treatment of hypertension have demonstrated that, in general, dual therapy combinations of ARBs plus a diuretic (either HCTZ or chlorthalidone) or amlodipine achieve greater reductions in blood pressure and higher blood pressure control rates compared to monotherapy regimens of ARBs, amlodipine or diuretics (Sachse et al, 2002; Neutel et al, 2006; Neutel et al, 2008; Neutel et al, 2012; Salerno et al, 2004; Chrysant et al, 2004; Chrysant et al, 2008; Littlejohn et al, 2009; Sharma et al, 2007[a]; Sharma et al, 2012; Destro et al, 2008; Philipp et al, 2007; Flack et al, 2009; Waeber et al, 2001; Zhu et al, 2012; Derosa et al, 2013). A meta-analysis by Conlin et al found that combination therapy with ARBs and HCTZ resulted in substantially greater reductions in systolic and diastolic blood pressure compared to ARB monotherapy (Conlin et al, 2000).
- Trials assessing triple therapy regimens with an ARB, amlodipine, and HCTZ demonstrate significantly greater blood pressure reductions with triple therapy compared to combination and monotherapy (Destro et al, 2010; Calhoun et al, 2009[a]; Calhoun et al, 2009[b]; Ohma et al, 2000; Wright et al, 2011).
- The safety and efficacy of nebivolol/valsartan 5/80 mg was based on a double-blinded, placebo-controlled, parallel-group, dose-escalating, Phase 3, randomized controlled trial in 4,159 patients with Stage 1 or 2 hypertension. Patients were randomized to 1 of 4 treatment arms (with a total of 7 dose groups plus placebo): (1) nebivolol/valsartan (5/80 mg, 5/160 mg, or 10/160 mg); (2) nebivolol monotherapy (5 mg or 20 mg); (3) valsartan monotherapy (160 mg or 320 mg); or (4) placebo. All treatment was administered in fixed doses once per day for 4 weeks; doses were then doubled for weeks 5 to 8 of treatment. Compared to placebo, nebivolol/valsartan 5/80 mg significantly lowered systolic blood pressure (SBP) by 8.3 mmHg and diastolic blood pressure (DBP) by 7.2 mmHg, monotherapy with nebivolol 5 mg lowered SBP by 4.7 mmHg and DBP by 4.4 mmHg, and monotherapy with valsartan 80 mg lowered SBP by 5.4 mmHg and DBP by 3.9 mmHg after 4 weeks of treatment. Higher doses of the combination did not lead to further clinically meaningful reductions in BP. No adverse events were observed more frequently with nebivolol/valsartan compared to placebo. As anticipated with beta blocker and ARB therapy, serious adverse reactions such as hypotension or hyperkalemia may occur (Giles et al, 2014).

- Head-to-head trials have not consistently demonstrated superiority of one combination product over another within the class (Ambrosioni et al, 2010; Bobrie et al, 2005; Cushman et al, 2012; Derosa et al, 2013; Fogari et al, 2006; Lacourcière et al, 2003; Ohma et al, 2000; Sharma et al, 2007[b]; Toh et al, 2016; White et al, 2008; Wright et al, 2011).

SAFETY SUMMARY

- ARB combinations are contraindicated in patients with hypersensitivity to any of the components. In general, ARB combinations with HCTZ are contraindicated in patients with anuria. ARB-containing products should not be administered in combination with aliskiren (TEKTURNA®).
- All ARB-containing products have a boxed warning that states that use during pregnancy should be avoided. When pregnancy is detected, discontinue the ARB combination as soon as possible. Drugs that act directly on the renin-angiotensin system (RAS) can cause injury and death to the developing fetus.
- Dual blockade of the RAS with ARBs, ACE-Is, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors.
- ARB-containing products may cause hypotension, electrolyte abnormalities, and renal impairment.
- Nebivolol/valsartan is also contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), and severe hepatic impairment.
- Common adverse events include hypotension, dizziness, headache, rash, pain, and cough.
- Edema is more commonly associated with amlodipine.
- Drug interactions with ARB-containing products include lithium (increase in lithium levels) and non-steroidal anti-inflammatory drugs (NSAIDs) (reduce ARB and diuretic effects and increased risk of renal injury or impairment). See prescribing information for full descriptions.
- Data from one controlled trial (ROADMAP) and an epidemiologic study (ORIENT) have suggested that high-dose BENICAR (olmesartan 40 mg daily) may increase cardiovascular (CV) risk in diabetic patients. The FDA safety review found no clear evidence of increased cardiovascular risks associated with olmesartan and determined the benefits outweighed the risks in patients with diabetes (BENICAR HCT prescribing information, 2016; Haller et al, 2011; Imai et al, 2011; FDA Drug Safety Communication: Safety Announcement, 2010; Safety Announcement, 2011; Safety Announcement, 2014).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ARB/Diuretic Combinations				
ATACAND HCT (candesartan/ HCTZ)	Tablet: 16/12.5 mg 32/12.5 mg 32/25 mg	Hypertension*: Initial: initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components.	Patients not controlled or experiencing hypokalemia on HCTZ 25 mg can expect an incremental effect from 16/12.5 mg; patients not controlled on candesartan 32 mg can expect incremental blood pressure effects from 32/12.5 mg and 32/25 mg.	May administer with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
AVALIDE (irbesartan/ HCTZ)	Tablet: 150/12.5 mg 300/12.5 mg	Hypertension†: Initial: 150/12.5 mg daily; may increase dose after 1 to 2 weeks to a maximum of 300/25 mg daily.	For patients not controlled on monotherapy with irbesartan or HCTZ, the recommended dose, in order of increasing mean effect, are 150/12.5, 300/12.5 and 300/25 mg.	May administer with or without food.
BENICAR HCT (olmesartan/ HCTZ)	Tablet: 20/12.5 mg 40/12.5 mg 40/25 mg	Hypertension*: Initial: initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components.	For patients not controlled on olmesartan, HCTZ may be added starting with a dose of 12.5 mg and later titrated to 25 mg daily; if patient is taking HCTZ, olmesartan may be added starting with a dose of 20 mg daily and titrated to 40 mg. Administer only one tablet daily.	-
DIOVAN HCT (valsartan/ HCTZ)	Tablet: 80/12.5 mg 160/12.5 mg 160/25 mg 320/12.5 mg 320/25 mg	Hypertension†: Initial: 160/25 mg daily; maximum, 320/25 mg daily.	Patients not controlled on valsartan or HCTZ monotherapy may switch to combination therapy.	-
EDARBYCLOR (azilsartan/ chlorthalidone)	Tablet: 40/12.5 mg 40/25 mg	Hypertension†: Initial: 40/12.5 mg daily. May increase dose to 40/25 mg after 2 to 4 weeks as needed to achieve blood pressure goals. Doses above 40/25 mg are probably not useful.	Patients not controlled with azilsartan may have an additional blood pressure reduction when switched to 40/12.5 mg. Patients not controlled with chlorthalidone 25 mg have further BP reduction when switched to 40/12.5 mg.	May administer with or without food.
HYZAAR (losartan/ HCTZ)	Tablet: 50/12.5 mg 100/12.5 mg 100/25 mg	Hypertension‡: Initial: 50/12.5 mg daily; maintenance, if blood pressure remains uncontrolled, the dose may be increased to 2 tablets of 50/12.5 mg daily or 1 tablet of	LV Hypertrophy with Hypertension§: If additional BP reduction is needed, losartan 100 mg and HCTZ 12.5 mg or 100/12.5 mg may be substituted, followed	May administer with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		100/25 mg daily; maximum, 100/25 mg/day. LV hypertrophy in hypertensive patients§: Initial: losartan 50 mg daily; if blood pressure is not adequately controlled, increase to 50/12.5 mg daily; maximum, 100/25 mg/day.	by losartan 100 mg and HCTZ 25 mg or 100/25 mg.	
MICARDIS HCT (telmisartan/ HCTZ)	Tablet: 40/12.5 mg 80/12.5 mg 80/25 mg	Hypertension*: Initial: initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components.	Patients not controlled on telmisartan 80 mg monotherapy may be switched to 80/12.5 mg daily and titrated up to 160/25 mg if necessary; patients not controlled on HCTZ 25 mg may be switched to 80/12.5 or 80/25 mg daily.	May administer with or without food.
ARB/Beta Blocker Combination				
BYVALSON (valsartan/ nebivolol)	Tablet: 80/5 mg	Hypertension†: Initial or in patient adequately controlled on valsartan ≤80 mg or nebivolol ≤10 mg: 80/5 mg once daily; maximum, 80/5 mg daily; combination may be substituted for the titrated individual components.	Maximum antihypertensive effects are attained within 2 to 4 weeks. BYVALSON is no recommended in severe renal impairment, pregnancy, or moderate hepatic impairment.	May administer with or without food.
ARB/CCB Combinations				
AZOR (olmesartan/ amlodipine)	Tablet: 20/5 mg 40/5 mg 20/10 mg 40/10 mg	Hypertension†: Initial: 20/5 mg daily; maximum, 40/10 mg daily; combination may be substituted for the titrated individual components.	Dosages may be increased after 2 weeks. Initial therapy with AZOR is not recommended in patients ≥75 years old or with hepatic impairment.	May administer with or without food.
EXFORGE (valsartan/ amlodipine)	Tablet: 160/5 mg 160/10 mg 320/5 mg 320/10 mg	Hypertension†: Initial: 160/5 mg daily; maximum, 320/10 mg daily; combination may be substituted for the	The dosage can be increased after 3 to 4 weeks of therapy to a maximum of one 320/10 mg tablet once daily as needed	May administer with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		titrated individual components.	to control blood pressure.	
TWYNSTA (telmisartan/ amlodipine)	Tablet: 40/5 mg 40/10 mg 80/5 mg 80/10 mg	Hypertension†: Initial: 40/5 mg daily, patients requiring larger blood pressure reductions may be started at 80/5 mg daily; combination may be substituted for the titrated individual components; maximum, 80/10 mg daily.	The dosage can be increased after at least 2 weeks to a maximum of 80/10 mg once daily.	May administer with or without food.
ARB/CCB/Diuretic Combinations				
EXFORGE HCT (valsartan/ amlodipine/ HCTZ)	Tablet: 160/5/12.5 mg 160/5/25 mg 160/10/12.5 mg 160/10/25 mg 320/10/25 mg	Hypertension*: Initial: initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components; maximum, 320/10/25 mg daily.	The dosage may be increased after 2 weeks of therapy. The full BP lowering effect was achieved 2 weeks after being on the maximal dose of EXFORGE HCT.	EXFORGE HCT may be used for patients not adequately controlled on any 2 of the following antihypertensive classes: calcium channel blockers, ARBs, and diuretics. May administer with or without food.
TRIBENZOR (olmesartan/ amlodipine/ HCTZ)	Tablet: 20/5/12.5 mg 40/5/12.5 mg 40/5/25 mg 40/10/12.5 mg 40/10/25 mg	Hypertension*: Initial: initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components; maximum, 40/10/25 mg.	The dosage can be increased after at least 2 weeks to a maximum of 40/10/25 mg once daily.	May be used for patients not adequately controlled on any 2 of the following antihypertensive classes: calcium channel blockers, ARBs, and diuretics. May administer with or without food.

*This fixed-dose combination is not indicated for initial therapy.
†Indicated to treat hypertension in patients not adequately controlled on monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
‡The fixed-dose combination is not indicated for initial therapy, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risks of initiating combination therapy in these patients.
§There is evidence that this benefit does not extend to African American patients.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
ARB/Diuretic Combinations					
ATACAND HCT (candesartan/ HCTZ)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	Safety and effectiveness in patients with severe renal impairment (CrCL ≤30 mL/min) have not been established.	Consider lower starting dose of 8 mg in patients with moderate hepatic impairment; however, this dose is not available with the HCTZ combination.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
AVALIDE (irbesartan/ HCTZ)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	In patients with CrCL ≤30 mL/min, loop diuretics are preferred to thiazides. AVALIDE is not recommended.	No dosage adjustment required.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
BENICAR HCT (olmesartan/ HCTZ)	Dosing should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased organ function and other diseases or drug therapy.	Safety and efficacy in children have not been established.	In patients with CrCL ≤30 mL/min, loop diuretics are preferred over HCTZ. BENICAR HCT is not recommended.	No dosage adjustment required.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
DIOVAN HCT (valsartan/ HCTZ)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	Safety and efficacy in patients with severe renal impairment (CrCL ≤30 mL/min) have not been established.	No dosage adjustment required. No data in severe hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
EDARBYCLOR (azilsartan/ chlorthalidone)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	No dosage adjustment required. Safety and effectiveness in patients with severe renal impairment (estimated GFR	No dosage adjustment required. Not studied in severe hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk;

Drug	Population and Precaution				
	Elderly	Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
			<30 mL/min/1.73 m^2) have not been established.		discontinue drug or nursing.
HYZAAR (losartan/HCTZ)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	In patients with CrCL ≤30 mL/min, loop diuretics are preferred to thiazides. HYZAAR is not recommended.	Not recommended in hepatic impairment as the lower starting dose of losartan is not available in HYZAAR.	Pregnancy Category: C (first trimester) Pregnancy Category: D (second and third trimester) Unknown whether excreted in breast milk; discontinue drug or nursing.
MICARDIS HCT (telmisartan/ HCTZ)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	In patients with CrCL ≤30 mL/min, loop diuretics are preferred to thiazides. MICARDIS HCT is not recommended.	Not recommended in severe hepatic impairment. Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision using the 40/12.5 mg dose.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
ARB/Beta Blocker Combination					
BYVALSON (valsartan/ nebivolol)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	No dosage adjustment required for mild to moderate renal impairment. Not recommended in severe renal impairment.	Not recommended in moderate to severe hepatic impairment.	Can cause fetal harm. Discontinue if pregnancy is detected. Beta blockers have potential to effect nursing infants; discontinue drug or nursing.
ARB/CCB Combinations					
AZOR (olmesartan/ amlodipine)	No dosage adjustment required in the elderly population. Initial therapy is not recom-mended in	Safety and efficacy in children have not been established.	No dosage adjustment required for mild to moderate renal impairment (CrCL<40 mL/min).	Use caution in patients with severe hepatic impairment. Initial therapy is not recommended in hepatically impaired patients.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.

Drug	Population and Precaution				
	Elderly	Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	patients ≥75 years of age.				
EXFORGE (valsartan/ amlodipine)	Consider lower doses in the elderly population.	Safety and efficacy in children have not been established.	Safety and effectiveness for CrCL <30 mL/min has not been established.	Lower initial doses of amlodipine may be required in patients with hepatic impairment. Not recommended for initial therapy.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
TWYNSTA (telmisartan/ amlodipine)	No dosage adjustment required in the elderly population. Initial therapy is not recom-mended in patients ≥75 years of age.	Safety and efficacy in children have not been established.	No dosage adjustment required.	Initiate amlodipine at 2.5 mg in patients with severe hepatic impairment. Initial therapy is not recommended in hepatically impaired patients. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in hepatically impaired patients.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
ARB/CCB/Diuretic Combinations					
EXFORGE HCT (valsartan/ amlodipine/ HCTZ)	Consider lower doses in the elderly population.	Safety and efficacy in children have not been established.	Safety and efficacy in patients with renal impairment (CrCL <30 mL/min) have not been established.	Lower starting doses of amlodipine may be required in patients with hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
TRIBENZOR (olmesartan/ amlodipine/ HCTZ)	No dosage adjustment required in the elderly population. Patients ≥75 years of age should start amlodipine at 2.5 mg, which is not available with TRIBENZOR.	Safety and efficacy in children have not been established.	No dosage adjustment required. Avoid use in patients with CrCL<30 mL/min.	Initiate amlodipine at 2.5 mg in patients with severe hepatic impairment, which is not available with TRIBENZOR. Initial therapy is not recommended in hepatically impaired patients.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.

Abbrv: CrCL=creatinine clearance, GFR=glomerular filtration rate, HCTZ=hydrochlorothiazide, LV=left ventricular

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category D = Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may justify the use of the drug in pregnant women despite potential risks.

CONCLUSION

- The ARB combination products are Food and Drug Administration (FDA)-approved for the treatment of hypertension. HYZAAR is also indicated for stroke prophylaxis in hypertensive patients with left ventricular hypertrophy.
- The products available in this class include various combinations of an ARB with a beta blocker (nebivolol), calcium channel blocker (amlodipine), chlorthalidone, a thiazide diuretic (HCTZ) or both HCTZ and amlodipine, and there are several generics available in this class.
- Losartan/hydrochlorothiazide (HCTZ) carries the additional indication of reduction in the risk of stroke in patients with hypertension and left ventricular hypertrophy.
- Losartan/HCTZ is the only combination agent in the class which carries an additional indication for reduction in the risk of stroke in patients with hypertension and left ventricular hypertrophy. The efficacy of losartan in preventing stroke in this population was demonstrated in the Losartan Intervention for Endpoint trial and its corresponding substudies. Losartan was compared to therapy with atenolol (HCTZ could be added to primary regimens if needed for blood pressure control). Results demonstrate a 24.9% relative risk reduction in stroke in patients treated with losartan-based regimens as compared to atenolol-based regimens (Dahlöf et al, 2002).
- Clinical trials assessing the ARB combination products in the treatment of hypertension have demonstrated that, in general, dual therapy combinations of ARBs plus either HCTZ, nebivolol, or amlodipine achieve greater reductions in blood pressure and higher blood pressure control rates compared to monotherapy regimens of ARBs, nebivolol, amlodipine or HCTZ. A meta-analysis by Conlin et al found that combination therapy with ARBs and HCTZ resulted in substantially greater reductions in systolic and diastolic blood pressure compared to ARB monotherapy (Conlin et al, 2000). Trials assessing triple therapy regimens with an ARB, amlodipine and HCTZ demonstrate significantly greater blood pressure reductions with triple therapy compared to combination and monotherapy (Destro et al, 2010; Calhoun et al, 2009[b]; Ohma et al, 2000). Head-to-head trials have not consistently demonstrated superiority of one combination product over another within the class (Ambrosioni et al, 2010; Bobrie et al, 2005; Fogari et al, 2006; Giles et al, 2014; Lacourcière et al, 2003; Ohma et al, 2000; Sharma et al, 2007[b]; White et al, 2008).
- Evidence-based guidelines recognize the important role ARBs, beta blockers, CCBs and diuretics play in the treatment of hypertension and other cardiovascular and renal diseases. There is no consensus on blood pressure goals for certain populations, such as older patients, patients with diabetes, and/or CKD. Combination therapy is recommended once the initial drug is titrated to maximum and the goal blood pressure is not reached (Go et al, 2014; James et al, 2013; Mancia et al, 2013; Weber et al, 2014). The guidelines also differ on first-line treatment options in various groups. Treatment is generally recommended based on agents in the class. The current treatment guidelines do not make recommendations based on combination therapy:
  - In black hypertensive patients, thiazide-type diuretics or CCBs are recommended as first line therapy and in non-black patients ACE-Is or ARBs, CCBs, and thiazides are options for initiating treatment, although some guidelines recommend ACE-Is or ARBs in non-black patients only (Go et al, 2014; James et al, 2013; Mancia et al, 2013; Piepoli et al, 2016; Rosendorff et al, 2015; Weber et al, 2014).
  - ACE-Is or ARBs are recommended as a first-line option in patients with chronic kidney disease (CKD) with or without proteinuria, due to its renal protective attributes. Combination therapy may be most useful in patients without electrolyte abnormalities and dihydropyridine CCBs may not be appropriate in patients with increased urinary albumin excretion (Go et al, 2014; Mancia et al, 2013; James et al, 2013; KDIGO, 2012; Weber et al, 2014).
  - ACE-Is or ARBs are also recommended as a first-line therapy option in heart failure, for patients post-myocardial infarction, and in cases of left ventricular dysfunction, unless otherwise contraindicated. (Anderson et al, 2007; Fox et al, 2006; Go et al, 2014; Hamm et al, 2011; Jneid et al, 2012; Lindenfeld et al, 2010; O'Gara et al, 2013; Montalescot et al, 2013; Ponikowski et al, 2016; Roffi et al, 2016; Steg et al, 2012; Stout et al, 2016; Weber et al, 2014; Windecker et al, 2014; Yancy et al, 2013; Yancy et al, 2016).
  - In general, reputable guidelines recommend the combination of a beta blocker and ARB as an option in patients with hypertension and coronary artery disease, post-MI regardless of BP, or HF (Go et al, 2014; James et al, 2013; Weber et al, 2014).

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