Therapeutic Class Overview
Renin Inhibitors and Combinations

INTRODUCTION

- Approximately 92.1 million American adults have at least one type of cardiovascular disease according to the 2017 American Heart Association Heart Disease and Stroke Statistics update. From 2004 to 2014, mortality associated with cardiovascular disease declined 25.3% (Benjamin et al, 2017).
- An estimated 85.7 million Americans or 34% of US adults aged ≥20 years 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 (Benjamin et al, 2017).
- Lowering of BP 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 (Benjamin et al, 2017).
- Aliskiren (TEKTURNA®) is the only single entity direct renin inhibitor available in the United States (U.S.) and is Food and Drug Administration (FDA)-approved for the treatment of hypertension, either as monotherapy or in combination with other antihypertensive agents.
- Currently, only one combination renin inhibitor product is available in the US. This product combines the direct renin inhibitor, aliskiren, with a thiazide diuretic (TEKTURNA-HCT®) and is approved for hypertension.
- Studies have demonstrated that the combination of two inhibitors of the renin angiotensin system (RAS), including aliskiren, an angiotensin converting enzyme inhibitor (ACE-I) or an angiotensin II receptor blocker (ARB), provide no renal or cardiovascular benefits, and significant adverse events, particularly in patients with diabetes and/or renal insufficiency. All agents in this class have safety warnings against combined use (Fried et al, 2013; ONTARGET Investigators, 2008; Parving et al, 2012; Pfeffer et al, 2003b; Sakata et al, 2015). Due to the results of these trials, Novartis AG also announced the market withdrawal of VALTURNA® (aliskiren/valsartan) effective in July 2012 (FDA Drug Safety Communication, 2012). More recently, two other combination products have been withdrawn from the market: TEKAMLO® (aliskiren/amlodipine) and AMTURNIDE® (aliskiren/amlodipine/hydrochlorothiazide).
- This review will focus on the direct renin inhibitors and combination agents which are FDA-approved to treat hypertension.
- Medispan class: Direct Renin Inhibitors; Direct Renin Inhibitors & Thiazide/Thiazide-like combinations

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
Single Entity Agent			
TEKTURNA (aliskiren)	Novartis	03/05/2007	-
Combination Agent			
TEKTURNA HCT (aliskiren/hydrochlorothiazide)	Novartis	01/18/2008	-

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	TEKTURNA (aliskiren)	TEKTURNA HCT (aliskiren/HCTZ)
Treatment of hypertension	✔	-
Treatment of hypertension as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals	-	✔
Treatment of hypertension in patients not adequately controlled with monotherapy	-	✔

Indication	TEKTURNA (aliskiren)	TEKTURNA HCT (aliskiren/HCTZ)
Treatment of hypertension as a substitute for the titrated components	-	✔

Abbrv: HCTZ=hydrochlorothiazide

(Prescribing information: TEKTURNA, 2016; TEKTURNA HCT, 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

- Aliskiren has been shown to lower BP to a greater degree than placebo and this effect is dose-dependent (Oh et al, 2007; Kushiro et al, 2006; Musini et al, 2017; Villa et al, 2012; Fortin et al, 2011).
- There are limited studies comparing aliskiren to other antihypertensive agents, including the ACE-Is and ARBs. These studies have generally demonstrated similar efficacy when administered in comparable doses and frequencies (Strasser et al, 2007; Duprez et al, 2010; Andersen et al, 2008; Zhu et al, 2012; Gradman et al, 2005; Krone et al, 2011; Stanton et al, 2003). In general, the incidence of side effects was also similar between treatment groups. One study reported better efficacy with aliskiren compared to ramipril, and a higher incidence of cough with ramipril (5.5%) compared to aliskiren (2.1%) (Andersen et al, 2008). A second study showed that after eight weeks of treatment, aliskiren was noninferior to ramipril in regard to antihypertensive effects on mean sitting diastolic blood pressure (DBP) (Zhu et al, 2012).
- One study compared aliskiren monotherapy to hydrochlorothiazide monotherapy and demonstrated significantly lower systolic (SBP) and DBP at weeks 6 and 12 with aliskiren in addition to better overall response rates; however, the significant difference in SBP was not maintained at week 52 (Schmieder et al, 2009a; Schmieder et al, 2009b).
- In separate studies, the combination of aliskiren/hydrochlorothiazide was shown to be significantly more effective than hydrochlorothiazide and aliskiren monotherapy at reducing SBP after 8 and 12 weeks, respectively (P<0.0001 compared to monotherapy in both studies). Similarly, greater improvements in DBP were also achieved with aliskiren/hydrochlorothiazide in both studies compared to treatment with monotherapy (P<0.0001 compared to monotherapy in both studies) (Basile et al, 2011; Black et al, 2010).
- In a randomized study, patients receiving treatment with aliskiren/hydrochlorothiazide or amlodipine monotherapy experienced a reduction in SBP from baseline to week 8, but no differences were observed between treatments (-28.6 vs -28.1 mm Hg for aliskiren/hydrochlorothiazide and amlodipine, respectively; P=0.8) (Ferdinand et al, 2011).
- A comparative effectiveness review evaluated ACE-Is, ARBs and aliskiren (Sanders et al, 2011). Two studies comparing ACE-Is with aliskiren demonstrated a greater reduction in BP with aliskiren compared to ramipril. One study compared aliskiren and losartan which showed no significant difference in BP reduction.
- The ASTRONAUT trial evaluated the effect of aliskiren in combination with standard therapy in heart failure (HF) patients hospitalized for worsening disease. Aliskiren did not result in a reduction in the primary endpoint of cardiovascular mortality or HF re-hospitalization at six months, or at 12 months (the secondary endpoint) (Gheorghiade et al, 2013). However, an ASTRONAUT substudy examined diabetic patient outcomes in the ASTRONAUT trial, and although there was no difference between diabetic and non-diabetic patient outcomes for the primary endpoint at 6 months, there was a statistically significant difference at 12 months, with less non-diabetic patients experiencing cardiovascular mortality or HF re-hospitalization. Results should be interpreted with caution as this was a sub-analysis of a statistically significant secondary outcome. Results insinuate that a larger trial excluding diabetic patients may provide more answers regarding treatment of patients with HF hospitalized for worsening disease (Maggioni et al, 2013).
- The termination of the ALTITUDE trial was due to an increased incidence of non-fatal stroke, renal complications, hyperkalemia, and hypotension in the aliskiren treatment arm when added to standard care in patients with type 2 diabetes and concomitant renal impairment. Novartis AG ceased promotion of aliskiren-containing products for use in combination with an ACE-I or ARB (Parving et al, 2012).
- Following the premature termination of the ALTITUDE study, the APOLLO study was also terminated. The APOLLO study included 11,000 elderly patients and was designed to examine the effects of aliskiren on cardiovascular events such as heart attack or stroke. Some patients were diabetic and taking ACE-Is or ARBs in combination with aliskiren,

which is included as a contraindication in current labeling. However, it is not completely clear if this is why the APOLLO study was terminated (Teo et al, 2014).

- According to the results from the ATMOSPHERE trial, aliskiren did not meet non-inferiority compared to enalapril for the composite outcome of death due to cardiovascular causes or hospitalization for heart failure in patients with chronic heart failure (McMurray et al, 2016). The combination of enalapril with aliskiren led to more hypotension, elevated serum creatinine, and elevated potassium levels compared to enalapril therapy without any benefits in the composite outcome.

SAFETY SUMMARY

- Avoid use of aliskiren-containing medications with ARBs or ACE-Is, particularly in patients with diabetes and/or moderate renal impairment (glomerular filtration rate [GFR] <60 mL/min).
- All agents in this class carry a boxed warning regarding use in pregnancy. When pregnancy is detected, discontinue aliskiren-containing products as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. Thiazides may cause fetal or neonatal jaundice, thrombocytopenia, and other adverse reactions.
- Symptomatic hypotension may occur after initiation of aliskiren in patients with an activated RAS, such as those who are volume- and/or salt-depleted. Correct those conditions prior to treatment. A transient hypotensive response does not contraindicate further treatment once blood pressure has been stabilized.
- Other warnings include risk of angioedema, worsening of renal function, and hyperkalemia.
- Concurrent use of aliskiren and cyclosporine or itraconazole results in a significant increase in blood concentrations of aliskiren. Concurrent use is not recommended.
- Hydrochlorothiazide is contraindicated in patients with known anuria or hypersensitivity to sulfonamide derived drugs like hydrochlorothiazide or to any of the components.
- Electrolyte imbalances may occur in patients on a combination containing hydrochlorothiazide.
- Common adverse events include dizziness and headache.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
TEKTURNA (aliskiren)	Tablet: 150 mg 300 mg	Treatment of HTN to lower BP: Initial, 150 mg daily; may increase daily dose to 300 mg daily if BP not adequately controlled	Establish a routine for the administration of aliskiren in relation to meal time. High fat meals reduce absorption.
TEKTURNA HCT (aliskiren/HCTZ)	Tablet: 150 mg/12.5 mg 150 mg/25 mg 300 mg/12.5 mg 300 mg/25 mg	Treatment of HTN to lower BP: Initial, 150 mg/12.5 mg daily; maximum, 300 mg/25 mg daily	Establish a routine for the administration of aliskiren in relation to meal time. High fat meals reduce absorption. Order of increasing mean effect are 150/12.5 mg, 150/25 mg or 300/12.5 mg, and 300/25 mg.

Abbrv: BP=blood pressure, HCTZ=hydrochlorothiazide, HTN=hypertension

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
TEKTURNA (aliskiren)	No dosage adjustment required in the elderly population; greater sensitivity of some elderly cannot be ruled out.	Safety and efficacy have not been established in pediatric patients <18 years.	Safety and effectiveness in patients with eGFR <30 mL/min have not been established.	No dosage adjustment required.	Can cause fetal harm; discontinue drug. It is unknown whether the drug is excreted in breast milk; breastfeeding is not recommended.
TEKTURNA HCT (aliskiren/ HCTZ)	No dosage adjustment required in the elderly population; greater sensitivity of some elderly cannot be ruled out	Safety and efficacy have not been established in pediatric patients <18 years.	Safety and effectiveness of patients with severe renal impairment with CrCL <30 mL/min have not been established.	Up-titrate slowly due to the HCTZ component; minor alterations in fluid and electrolyte balance may precipitate hepatic coma.	Can cause fetal harm; discontinue drug. Thiazides are excreted in human milk; It is unknown whether aliskiren is excreted in human milk; breastfeeding is not recommended.

Abbrv: CrCL = creatinine clearance; eGFR = estimated glomerular filtration rate; HCTZ = hydrochlorothiazide

CONCLUSION

- Aliskiren is the only single-entity direct renin inhibitor marketed in the United States. Aliskiren is FDA-approved for the treatment of hypertension. The only currently available renin inhibitor combination (TEKTURNA-HCT®) is also FDA-approved for the treatment of hypertension. Previously available combination products including AMTURNIDE®, TEKAMLO®, and VALTURNA® have all been removed from the market.
- Aliskiren-containing products are contraindicated for use in combination with an ACE-I or ARB in patients with diabetes and/or those with moderate renal impairment. Aliskiren and thiazide diuretics are not recommended for use during pregnancy.
- Clinical trials have demonstrated that aliskiren 150 mg to 300 mg once daily is significantly more effective than placebo in lowering both SBP and DBP in men and women with mild-to-moderate essential hypertension (Musini et al, 2017; Kushiro et al, 2006; Oh et al, 2007).
- Limited lower quality comparative studies of aliskiren with other antihypertensive agents have generally demonstrated similar efficacy when administered in comparable doses (Strasser et al, 2007; Duprez et al, 2010; Andersen et al, 2008; Zhu et al, 2012; Gradman et al, 2005; Krone et al, 2011; Stanton et al, 2003). In general, the incidence of side effects was also comparable. Aliskiren alone or in combination with enalapril does not display any benefits in patients with chronic heart failure compared to enalapril therapy.
- Most hypertension guidelines do not address the use of aliskiren, specifically outside of labeled recommendations (Go et al, 2014; James et al, 2013; Weber et al, 2014). The 2013 European Society of Hypertension/European Society of Cardiology Guidelines (ESH/ESC) hypertension guidelines state that the use of aliskiren in the treatment of hypertension is justified based on available evidence. Available evidence shows that aliskiren monotherapy lowers

SBP and DBP, and a greater hypertensive effect is achieved when given in combination with a thiazide. Prolonged administration of combination therapy has a favorable effect on asymptomatic organ damage, or prognostic biomarkers for heart failure, such as BNP. Although, no trial data is available for the effect of aliskiren on cardiovascular and renal morbidity and fatal events in hypertension (Mancia et al, 2013).

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