ALISKIREN

DRUGDEX 评估

DOSING/ADMINISTRATION

Adult Dosing

Normal Dosage

Oral route

Chronic kidney disease, Nondiabetic

a) Dose: 150 mg orally once daily [5]

Diabetic nephropathy - Hypertension

a) Off-label dosage: 150 [1][2][3] or 300 mg orally daily [4][2][3]

Hypertension

a) Initial dosage: 150 mg orally once daily; take consistently with regard to meals [6].

b) Titration: The dose may be increased to 300 mg once daily if the blood pressure is not adequately controlled. While doses above 300 mg did not result in increased blood pressure response, they increased the rate of diarrhea in clinical trials [6].

Dosage in Renal Failure

A) No adjustments are necessary; however, safety and effectiveness have not been established in patients with a CrCl less than 30 mL/min [6].

Dosage in Hepatic Insufficiency

A) Mild to severe impairment: No initial adjustments are necessary [6].

Dosage in Geriatric Patients

A) No initial dosage adjustments are necessary [15].

Dosage Adjustment During Dialysis

A) Hemodialysis

1) ESRD: No dosage adjustment is necessary [6].

Pediatric Dosing

Normal Dosage

Oral route

Hypertension

a) 6 to 17 Years and 20 to 50 kg

1) Initial dosage: 75 mg orally once daily; take consistently with regard to meals [6].

2) Maximum dosage: 150 mg once daily [6]

b) 6 to 17 Years and 50 kg or Greater

1) Initial dosage: 150 mg orally once daily. Take consistently with regard to meals [6].

2) Titration: The dose may be increased to 300 mg once daily if the blood pressure is not adequately controlled. While doses above 300 mg did not result in increased blood pressure response, they increased the rate of diarrhea in clinical trials [6].

Dosage in Renal Failure

A) No adjustments are necessary; however, no data is available in pediatric patients with a GFR less than 30 mL/min/1.73m(2) [6].

Dosage in Hepatic Insufficiency

A) Mild to severe impairment: No initial adjustments are necessary [6].

Dosage Adjustment During Dialysis

A) Hemodialysis
1) ESRD: No dosage adjustment is necessary [6].

FDA Uses

Hypertension

FDA Labeled Indication
1) Overview
FDA Approval: Adult, yes; Pediatric, yes (6 years or older)
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category A; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Indication
Aliskiren is indicated for the treatment of hypertension [6].

Evidence (Adult)
Aliskiren monotherapy significantly lowers blood pressure (BP) compared with placebo [7] and to a similar extent compared with losartan [8] or irbesartan [9]. Doses above aliskiren 300 mg/day have not resulted in additional BP response, but have increased the rate of diarrhea [6]. Additional BP reduction was achieved in combination with atenolol [10], hydrochlorothiazide [11], and valsartan [12][13]; however, in 1 study a higher incidence of elevated serum potassium levels and elevated serum creatinine were observed when aliskiren was used in combination with valsartan [12].

Evidence (Pediatric)
Weight-based dosing of aliskiren led to reductions in systolic and diastolic blood pressure in pediatric patients. Reductions were similar to those achieved with enalapril [6].

Guidelines (Adult)
Aliskiren, a direct renin inhibitor, is not a first-line agent for the treatment of hypertension. It is preferable to use a thiazide-type diuretic, a calcium channel blocker (CCB), an ACE inhibitor (ACEI), or an angiotensin receptor blocker (ARB) as initial antihypertensive therapy [14].

Simultaneous use of an ACE inhibitor, ARB, or direct renin inhibitor is not recommended for treatment of hypertension and is potentially harmful [14].

3) Adult:
a) Monotherapy
Monotherapy with aliskiren had a greater effect on lowering blood pressure (BP) compared with placebo in patients with mild to moderate hypertension in 6 randomized 8-week studies. Aliskiren (n=2730) at doses of 75 to 600 mg/day or placebo (n=1231) for 8 weeks resulted in clinically significant effects at the 150- and 300-mg doses, but no clear further increase was noted at the 600-mg dose. In some studies, ambulatory BP monitoring showed reasonable control throughout the interdosing interval and the ratio of mean daytime to nighttime BP ranged from 0.6 to 0.9. Continuation of open-label aliskiren or placebo for up to a year demonstrated a persistent BP lowering effect with a significant difference between patients maintained on aliskiren versus those on placebo (data not available). Cessation of therapy resulted in return to baseline BP values gradually over several week. Rebound hypertension did not occur in cases of abrupt cessation of therapy. BP lowering results of the 6 randomized studies are shown in the table below [7]:

		Aliskiren daily dose (mg)			
	Mean change (SBP/DBP) mmHg	Placebo-subtracted mean change (SBP/DBP) mmHg			
Study	Placebo	75 mg	150 mg	300 mg	600 mg
1	2.9/3.3	5.7/4*	5.9/4.5*	11.2/7.5*	--
2	5.3/6.3	--	6.1/2.9*	10.5/5.4*	10.4/5.2*
3	10/8.6	2.2/1.7	2.1/1.7	5.1/3.7*	--
4	7.5/6.9	1.9/1.8	4.8/2*	8.3/3.3*	--
5	3.8/4.9	--	9.3/5.4*	10.9/6.2*	12.1/7.6*
6	4.6/4.1	--	--	8.4/4.9*	--
Key: SBP = systolic blood pressure; DBP = diastolic blood pressure; * p < 0.05 versus placebo					

1) In a 4-week randomized trial in patients with mild-to-moderate hypertension (N=226), once-daily aliskiren 75 mg, 150 mg, and 300 mg were not significantly different than losartan 100 mg once-daily in lowering daytime ambulatory systolic blood pressure (SBP). The mean changes in SBP were -0.4 mmHg, -5.3 mmHg, -8 mmHg, and -11, respectively [8].

2) In an 8-week randomized trial in patients with mild-to-moderate hypertension (N=652) , aliskiren 150 mg once-daily was as effective as irbesartan 150 mg once-daily and superior to placebo in lowering BP. Patients received daily aliskiren (150, 300, or 600 mg), irbesartan 150 mg, or placebo. Aliskiren 150 mg, 300 mg, and 600 mg lowered SBP/DBP 11.4/9.3 mmHg, 15.8/11.8 mmHg, and 15.7/11.5 mmHg, respectively. This was significant compared with the SBP/DBP lowering of placebo (5.3/6.3 mmHg). Aliskiren lowered DBP, but not SBP, significantly more than irbesartan 150 mg (12.5/8.9 mmHg) at the 300- and 600-mg doses. Aliskiren 600 mg daily had no blood pressure reductions beyond that of aliskiren 300 mg daily [9].

b) Combination Therapy

1) With Atenolol

a) Combination aliskiren 150 mg and atenolol 50 mg significantly lowered mean sitting diastolic BP (DBP) by 2.9 mmHg compared with aliskiren 300 mg monotherapy in a randomized study (N=694). There was no significant difference between the combination and atenolol 100 mg/day. Atenolol 100 mg decreased DBP significantly more than aliskiren 300 mg (difference, 2.4 mmHg). The difference in systolic BP (SBP) lowering was significant for the combination compared with both aliskiren 300 mg (-2.9 mmHg) and atenolol 100 mg (-3 mmHg); although, the difference between aliskiren and atenolol was not significant. In the combination group, 51.3% achieved blood pressure control (defined as less than 140/90 mmHg), significantly better than either monotherapy (aliskiren 36.1%; atenolol 42.2%). Bradycardia was reported only in the atenolol (2.2%) and combination (1.3%) groups and 2 patients in each of those groups discontinued the study due to the adverse event. A pulse rate below 55 beats per minute occurred significantly more often in both atenolol and combination treatment groups compared with aliskiren monotherapy (aliskiren 1.9%; atenolol 13%; combination 10.1%). Serious adverse events occurred at a similar rate in all groups (aliskiren 2.2%; atenolol 3%; combination 0.9%) [10]

Blood Pressure Measurements	Aliskiren 300 mg (n=231)	Atenolol 100 mg (n=231)	Aliskiren 300 mg/ Atenolol 100 mg (n=232)
Diastolic Blood Pressure (DBP)			
Baseline DBP (mmHg)	99.7	99.3	99.5
Mean Change at Endpoint (mmHg)	-11.3	-13.7	-14.1
Result versus Aliskiren 300 mg	---	significant	significant
Result versus Atenolol 100 mg	significant	---	NS
Systolic Blood Pressure (SBP)			
Baseline SBP (mmHg)	157.6	155.7	157.4
Mean Change at Endpoint	-14.3	-14.3	-17.3
Result versus Aliskiren 300 mg	---	NS	significant
Result versus Atenolol 100 mg	NS	---	significant
KEY: NS, not significant			

2) With Hydrochlorothiazide

a) In an 8-week randomized trial (N=2752), aliskiren monotherapy at 150-mg and 300-mg dose levels was more effective than placebo in reducing blood pressure among adults with mild-to-moderate essential hypertension, and the combination use with hydrochlorothiazide provided additional blood pressure reduction. Treatment groups included aliskiren monotherapy (75, 150, or 300 mg), hydrochlorothiazide monotherapy (6.25, 12.5, or 25 mg), or aliskiren/hydrochlorothiazide combinations (except 300/6.25 mg). Aliskiren monotherapy led to a dose-related reduction in the mean sitting SBP (-9.4, -12.2, and -15.7 mmHg at the 75-, 150-, and 300-mg dose levels, respectively) and the mean sitting DBP (-8.7, -8.9, and -10.3 mmHg, respectively) versus -7.5/-6.9 mmHg in SBP/DBP change with placebo; however, only the 150- and 300-mg doses were significantly superior to placebo. The combination use of aliskiren and hydrochlorothiazide was significantly more effective than placebo and significantly more effective than either component of monotherapy; however, neither combination of aliskiren/hydrochlorothiazide 150/6.25 mg or 75/12.5 mg were significantly different relative to either monotherapy (-21.2/-14.3 mmHg with aliskiren/hydrochlorothiazide 300/25 mg combination vs -15.7/-10.3 mmHg with aliskiren 300 mg vs -14.3/-9.4 mmHg with hydrochlorothiazide 25 mg). The use of combination therapy led to a significantly higher response rate (achievement of DBP less than 90 mmHg and/or at least 10 mmHg DBP reduction from baseline) than placebo at study end (58.4% to 80.6% vs 45.8%) and a significantly larger proportion of patients achieving SBP/DBP less than 140/90 mmHg (37.4% to 59.5% vs 28.1%) except for aliskiren/hydrochlorothiazide 75/6.25 mg. Headache (7.2%) and nasopharyngitis (3.8%) were the most frequently reported adverse effects, and the overall adverse event rates were comparable amongst active treatment groups [11].

3) With Valsartan

a) In an 8-week randomized trial (n=1776), monotherapy with aliskiren or valsartan was significantly more effective than placebo in reducing blood pressure (BP) among adults with hypertension, and the combination use with aliskiren and valsartan was associated with additional BP lowering. Aliskiren monotherapy 150 mg, valsartan monotherapy 160 mg, combination of aliskiren 150 mg and valsartan 160 mg, or matching placebo were administered once daily for 4 weeks. The initial treatment dose was doubled, and maintained for another 4 weeks. All treatment groups significantly reduced the mean sitting diastolic BP (DBP) at week 8 from baseline: mean change, -9 mmHg for aliskiren, -9.7 mmHg for valsartan, -12.2 mmHg for aliskiren/valsartan, and -4.1 mmHg for placebo. The mean change in sitting systolic BP (SBP) was -13 mmHg for aliskiren, -12.8 mmHg for valsartan, -17.2 mmHg for aliskiren/valsartan, and -4.6 mmHg for placebo, respectively; all significant versus placebo. The blood pressure lowering was evident at 4 weeks while patients were treated with low doses. All treatment groups achieved significantly improved blood pressure control (a mean SBP/DBP less than 140/90 mmHg) compared with the placebo group (16%) at 8 weeks; and a significantly larger proportion of patients receiving combination therapy compared with those receiving aliskiren (49% vs 37%) or valsartan monotherapy (49% vs 34%) reached blood pressure goals. While the combination use of aliskiren and valsartan was associated with additional blood pressure lowering versus either agent alone, it was also associated with higher incidence of elevated serum potassium levels (greater than 5.5 mmol/L) (4% vs 2%), and elevated serum creatinine (greater than 176.8 micromol/L or 2 mg/dL (0.9% vs 0.2% to 0.4%) relative to either monotherapy [12].

b) In an 8-week randomized trial, aliskiren provided dose-related antihypertensive efficacy alone and in combination with valsartan in patients with mild-to-moderate hypertension who received once daily treatment with placebo (n=177), aliskiren monotherapy (75 mg (n=179), 150 mg (n=178), or 300 mg (n=175)), valsartan monotherapy (80 mg (n=58), 160 mg (n=59), or 320 mg (n=60)), combination aliskiren/valsartan (75/80 mg (n=60), 150/160 mg (n=60), or 300/320 mg (n=58)), or combination valsartan/hydrochlorothiazide (160/12.5 mg (n=59)). Aliskiren 300 mg orally once daily significantly lowered the mean sitting DBP relative to placebo (-12.3 vs -8.6 mmHg). The mean sitting systolic blood pressure (SBP) also was significantly lowered with aliskiren relative to placebo (-15 vs -10 mmHg). Reductions in mean sitting DBP and mean sitting SBP for aliskiren 75 mg and 150 mg were not significant relative to placebo. All 3 aliskiren/valsartan combinations significantly lowered mean sitting DBP and mean sitting SBP compared with placebo. The placebo-corrected mean change in DBP and SBP for aliskiren 150 mg/valsartan 160 mg was -3.48 and -6.66, respectively. Aliskiren 300 mg/valsartan 320 mg produced a placebo-corrected mean change in DBP and SBP of -4.34 and -8.07, respectively. Reductions in mean sitting DBP and mean sitting SBP with valsartan 160 mg/hydrochlorothiazide 12.5 mg were not significantly different from those found with either aliskiren 150 mg/valsartan 160 mg or aliskiren 300 mg/valsartan 320 mg. Aliskiren and valsartan were well tolerated in combination and in monotherapy; the rate of discontinuation and the incidence of adverse effects were similar to placebo in all of the treatment groups. The large antihypertensive effect seen with placebo (-8.6 +/- 0.62 for mean sitting DBP; -10.0 +/- 0.96 for mean sitting SBP) is a major limitation of this study. Another limitation is that this study was not powered to compare the combinations with their respective monotherapies [13].

4) Pediatric:

a) Systolic and diastolic blood pressure (BP) were reduced in a weight-based dose-dependent manner in pediatric patients 6 to 17 years of age with hypertension in a randomized trial (N=267). Sitting systolic BP reductions from baseline over 4 weeks were 4.8 mmHg with

aliskiren doses between 6.25 and 25 mg (low-dose group), 5.6 mmHg with doses between 37.5 and 150 mg (mid-dose group), and 8.7 mmHg with doses between 150 and 600 mg (high-dose group). In a 4-week withdrawal phase, the difference in mean change in sitting systolic BP between high-dose aliskiren and placebo was -2.7 mmHg. Note that doses above 300 mg have not been approved for pediatric patients [6].

b) In a 52-week randomized extension study (N=208), systolic/diastolic BP reduction was 7.6/3.9 mmHg with aliskiren compared with 7.9/4.9 mmHg with enalapril. Patients received weight-based dosing of aliskiren with an initial dose of 37.5 mg (20 to less than 50 kg), 75 mg (50 to less than 80 kg), or 150 mg (80 to 150 kg). Weight-based doses of enalapril were initiated at 2.5 mg (20 to less than 50 kg), 5 mg (50 to less than 80 kg), or 10 mg (80 to 150 kg). Optional dose up-titration was allowed for control of BP, with maximal doses based on weight categories of 20 to less than 50 kg (aliskiren, 150 mg; enalapril, 10 mg), 50 to less than 80 kg (aliskiren, 300 mg; enalapril, 20 mg), and 80 to 150 kg (aliskiren, 600 mg (not an approved dose); enalapril, 40 mg) [6].

Labeled Uses

Hypertension

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (6 years or older)

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category A; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indication

Aliskiren is indicated for the treatment of hypertension [6].

Evidence (Adult)

Aliskiren monotherapy significantly lowers blood pressure (BP) compared with placebo [7] and to a similar extent compared with losartan [8] or irbesartan [9]. Doses above aliskiren 300 mg/day have not resulted in additional BP response, but have increased the rate of diarrhea [6]. Additional BP reduction was achieved in combination with atenolol [10], hydrochlorothiazide [11], and valsartan [12][13]; however, in 1 study a higher incidence of elevated serum potassium levels and elevated serum creatinine were observed when aliskiren was used in combination with valsartan [12].

Evidence (Pediatric)

Weight-based dosing of aliskiren led to reductions in systolic and diastolic blood pressure in pediatric patients. Reductions were similar to those achieved with enalapril [6].

Guidelines (Adult)

Aliskiren, a direct renin inhibitor, is not a first-line agent for the treatment of hypertension. It is preferable to use a thiazide-type diuretic, a calcium channel blocker (CCB), an ACE inhibitor (ACEI), or an angiotensin receptor blocker (ARB) as initial antihypertensive therapy [14].

Simultaneous use of an ACE inhibitor, ARB, or direct renin inhibitor is not recommended for treatment of hypertension and is potentially harmful [14].

3) Adult:

a) Monotherapy

Monotherapy with aliskiren had a greater effect on lowering blood pressure (BP) compared with placebo in patients with mild to moderate hypertension in 6 randomized 8-week studies. Aliskiren (n=2730) at doses of 75 to 600 mg/day or placebo (n=1231) for 8 weeks resulted in clinically significant effects at the 150- and 300-mg doses, but no clear further increase was noted at the 600-mg dose. In some studies, ambulatory BP monitoring showed reasonable control throughout the interdosing interval and the ratio of mean daytime to nighttime BP ranged from 0.6 to 0.9. Continuation of open-label aliskiren or placebo for up to a year demonstrated a persistent BP lowering effect with a significant difference between patients maintained on aliskiren versus those on placebo (data not available). Cessation of therapy resulted in return to baseline BP values gradually over several week. Rebound hypertension did not occur in cases of abrupt cessation of therapy. BP lowering results of the 6 randomized

studies are shown in the table below [7]:

		Aliskiren daily dose (mg)			
	Mean change (SBP/DBP) mmHg	Placebo-subtracted mean change (SBP/DBP) mmHg			
Study	Placebo	75 mg	150 mg	300 mg	600 mg
1	2.9/3.3	5.7/4*	5.9/4.5*	11.2/7.5*	--
2	5.3/6.3	--	6.1/2.9*	10.5/5.4*	10.4/5.2*
3	10/8.6	2.2/1.7	2.1/1.7	5.1/3.7*	--
4	7.5/6.9	1.9/1.8	4.8/2*	8.3/3.3*	--
5	3.8/4.9	--	9.3/5.4*	10.9/6.2*	12.1/7.6*
6	4.6/4.1	--	--	8.4/4.9*	--
Key: SBP = systolic blood pressure; DBP = diastolic blood pressure; * p < 0.05 versus placebo					

1) In a 4-week randomized trial in patients with mild-to-moderate hypertension (N=226), once-daily aliskiren 75 mg, 150 mg, and 300 mg were not significantly different than losartan 100 mg once-daily in lowering daytime ambulatory systolic blood pressure (SBP). The mean changes in SBP were -0.4 mmHg, -5.3 mmHg, -8 mmHg, and -11, respectively [8].

2) In an 8-week randomized trial in patients with mild-to-moderate hypertension (N=652) , aliskiren 150 mg once-daily was as effective as irbesartan 150 mg once-daily and superior to placebo in lowering BP. Patients received daily aliskiren (150, 300, or 600 mg), irbesartan 150 mg, or placebo. Aliskiren 150 mg, 300 mg, and 600 mg lowered SBP/DBP 11.4/9.3 mmHg, 15.8/11.8 mmHg, and 15.7/11.5 mmHg, respectively. This was significant compared with the SBP/DBP lowering of placebo (5.3/6.3 mmHg). Aliskiren lowered DBP, but not SBP, significantly more than irbesartan 150 mg (12.5/8.9 mmHg) at the 300- and 600-mg doses. Aliskiren 600 mg daily had no blood pressure reductions beyond that of aliskiren 300 mg daily [9].

b) Combination Therapy

1) With Atenolol

a) Combination aliskiren 150 mg and atenolol 50 mg significantly lowered mean sitting diastolic BP (DBP) by 2.9 mmHg compared with aliskiren 300 mg monotherapy in a randomized study (N=694). There was no significant difference between the combination and atenolol 100 mg/day. Atenolol 100 mg decreased DBP significantly more than aliskiren 300 mg (difference, 2.4 mmHg). The difference in systolic BP (SBP) lowering was significant for the combination compared with both aliskiren 300 mg (-2.9 mmHg) and atenolol 100 mg (-3 mmHg); although, the difference between aliskiren and atenolol was not significant. In the combination group, 51.3% achieved blood pressure control (defined as less than 140/90 mmHg), significantly better than either monotherapy (aliskiren 36.1%; atenolol 42.2%). Bradycardia was reported only in the atenolol (2.2%) and combination (1.3%) groups and 2 patients in each of those groups discontinued the study due to the adverse event. A pulse rate below 55 beats per minute occurred significantly more often in both atenolol and combination treatment groups compared with aliskiren monotherapy (aliskiren 1.9%; atenolol 13%; combination 10.1%). Serious adverse events occurred at a similar rate in all groups (aliskiren 2.2%; atenolol 3%; combination 0.9%) [10]

Blood Pressure Measurements	Aliskiren 300 mg (n=231)	Atenolol 100 mg (n=231)	Aliskiren 300 mg/ Atenolol 100 mg (n=232)
Diastolic Blood Pressure (DBP)			
Baseline DBP (mmHg)	99.7	99.3	99.5
Mean Change at Endpoint (mmHg)	-11.3	-13.7	-14.1
Result versus Aliskiren 300 mg	---	significant	significant
Result versus Atenolol 100 mg	significant	---	NS
Systolic Blood Pressure (SBP)			
Baseline SBP (mmHg)	157.6	155.7	157.4
Mean Change at Endpoint	-14.3	-14.3	-17.3
Result versus Aliskiren 300 mg	---	NS	significant
Result versus Atenolol 100 mg	NS	---	significant
KEY: NS, not significant			

2) With Hydrochlorothiazide

a) In an 8-week randomized trial (N=2752), aliskiren monotherapy at 150-mg and 300-mg dose levels was more effective than placebo in reducing blood pressure among adults with mild-to-moderate essential hypertension, and the combination use with hydrochlorothiazide provided additional blood pressure reduction. Treatment groups included aliskiren monotherapy (75, 150, or 300 mg), hydrochlorothiazide monotherapy (6.25, 12.5, or 25 mg), or aliskiren/hydrochlorothiazide combinations (except 300/6.25 mg). Aliskiren monotherapy led to a dose-related reduction in the mean sitting SBP (-9.4, -12.2, and -15.7 mmHg at the 75-, 150-, and 300-mg dose levels, respectively) and the mean sitting DBP (-8.7, -8.9, and -10.3 mmHg, respectively) versus -7.5/-6.9 mmHg in SBP/DBP change with placebo; however, only the 150- and 300-mg doses were significantly superior to placebo. The combination use of aliskiren and hydrochlorothiazide was significantly more effective than placebo and significantly more effective than either component of monotherapy; however, neither combination of aliskiren/hydrochlorothiazide 150/6.25 mg or 75/12.5 mg were significantly different relative to either monotherapy (-21.2/-14.3 mmHg with aliskiren/hydrochlorothiazide 300/25 mg combination vs -15.7/-10.3 mmHg with aliskiren 300 mg vs -14.3/-9.4 mmHg with hydrochlorothiazide 25 mg). The use of combination therapy led to a significantly higher response rate (achievement of DBP less than 90 mmHg and/or at least 10 mmHg DBP reduction from baseline) than placebo at study end (58.4% to 80.6% vs 45.8%) and a significantly larger proportion of patients achieving SBP/DBP less than 140/90 mmHg (37.4% to 59.5% vs 28.1%) except for aliskiren/hydrochlorothiazide 75/6.25 mg. Headache (7.2%) and nasopharyngitis (3.8%) were the most frequently reported adverse effects, and the overall adverse event rates were comparable amongst active treatment groups [11].

3) With Valsartan

a) In an 8-week randomized trial (n=1776), monotherapy with aliskiren or valsartan was significantly more effective than placebo in reducing blood pressure (BP) among adults with hypertension, and the combination use with aliskiren and valsartan was associated with additional BP lowering. Aliskiren monotherapy 150 mg, valsartan monotherapy 160 mg, combination of aliskiren 150 mg and valsartan 160 mg, or matching placebo were administered once daily for 4 weeks. The initial treatment dose was doubled, and maintained for another 4 weeks. All treatment groups significantly reduced the mean sitting diastolic BP (DBP) at week 8 from baseline: mean change, -9 mmHg for aliskiren, -9.7 mmHg for valsartan, -12.2 mmHg for aliskiren/valsartan, and -4.1 mmHg for placebo. The mean change in sitting systolic BP (SBP) was -13 mmHg for aliskiren, -12.8 mmHg for valsartan, -17.2 mmHg for aliskiren/valsartan, and -4.6 mmHg for placebo, respectively; all significant versus placebo. The blood pressure lowering was evident at 4 weeks while patients were treated with low doses. All treatment groups achieved significantly improved blood pressure control (a mean SBP/DBP less than 140/90 mmHg) compared with the placebo group (16%) at 8 weeks; and a significantly larger proportion of patients receiving combination therapy compared with those receiving aliskiren (49% vs 37%) or valsartan monotherapy (49% vs 34%) reached blood pressure goals. While the combination use of aliskiren and valsartan was associated with additional blood pressure lowering versus either agent alone, it was also associated with higher incidence of elevated serum potassium levels (greater than 5.5 mmol/L) (4% vs 2%), and elevated serum creatinine (greater than 176.8 micromol/L or 2 mg/dL (0.9% vs 0.2% to 0.4%) relative to either monotherapy [12].

b) In an 8-week randomized trial, aliskiren provided dose-related antihypertensive efficacy alone and in combination with valsartan in patients with mild-to-moderate hypertension who received once daily treatment with placebo (n=177), aliskiren monotherapy (75 mg (n=179), 150 mg (n=178), or 300 mg (n=175)), valsartan monotherapy (80 mg (n=58), 160 mg (n=59), or 320 mg (n=60)), combination aliskiren/valsartan (75/80 mg (n=60), 150/160 mg (n=60), or 300/320 mg (n=58)), or combination valsartan/hydrochlorothiazide (160/12.5 mg (n=59)). Aliskiren 300 mg orally once daily significantly lowered the mean sitting DBP relative to placebo (-12.3 vs -8.6 mmHg). The mean sitting systolic blood pressure (SBP) also was significantly lowered with aliskiren relative to placebo (-15 vs -10 mmHg). Reductions in mean sitting DBP and mean sitting SBP for aliskiren 75 mg and 150 mg were not significant relative to placebo. All 3 aliskiren/valsartan combinations significantly lowered mean sitting DBP and mean sitting SBP compared with placebo. The placebo-corrected mean change in DBP and SBP for aliskiren 150 mg/valsartan 160 mg was -3.48 and -6.66, respectively. Aliskiren 300 mg/valsartan 320 mg produced a placebo-corrected mean change in DBP and SBP of -4.34 and -8.07, respectively. Reductions in mean sitting DBP and mean sitting SBP with valsartan 160 mg/hydrochlorothiazide 12.5 mg were not significantly different from those found with either aliskiren 150 mg/valsartan 160 mg or aliskiren 300 mg/valsartan 320 mg. Aliskiren and valsartan were well tolerated in combination and in monotherapy; the rate of discontinuation and the incidence of adverse effects were similar to placebo in all of the treatment groups. The large antihypertensive effect seen with placebo (-8.6 +/- 0.62 for mean sitting DBP; -10.0 +/- 0.96 for mean sitting SBP) is a major limitation of this study. Another limitation is that this study was not powered to compare the combinations with their respective monotherapies [13].

4) Pediatric:

a) Systolic and diastolic blood pressure (BP) were reduced in a weight-based dose-dependent manner in pediatric patients 6 to 17 years of age with hypertension in a randomized trial

(N=267). Sitting systolic BP reductions from baseline over 4 weeks were 4.8 mmHg with aliskiren doses between 6.25 and 25 mg (low-dose group), 5.6 mmHg with doses between 37.5 and 150 mg (mid-dose group), and 8.7 mmHg with doses between 150 and 600 mg (high-dose group). In a 4-week withdrawal phase, the difference in mean change in sitting systolic BP between high-dose aliskiren and placebo was -2.7 mmHg. Note that doses above 300 mg have not been approved for pediatric patients [6].

b) In a 52-week randomized extension study (N=208), systolic/diastolic BP reduction was 7.6/3.9 mmHg with aliskiren compared with 7.9/4.9 mmHg with enalapril. Patients received weight-based dosing of aliskiren with an initial dose of 37.5 mg (20 to less than 50 kg), 75 mg (50 to less than 80 kg), or 150 mg (80 to 150 kg). Weight-based doses of enalapril were initiated at 2.5 mg (20 to less than 50 kg), 5 mg (50 to less than 80 kg), or 10 mg (80 to 150 kg). Optional dose up-titration was allowed for control of BP, with maximal doses based on weight categories of 20 to less than 50 kg (aliskiren, 150 mg; enalapril, 10 mg), 50 to less than 80 kg (aliskiren, 300 mg; enalapril, 20 mg), and 80 to 150 kg (aliskiren, 600 mg (not an approved dose); enalapril, 40 mg) [6].

Non-FDA Uses

Chronic kidney disease, Nondiabetic

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In a retrospective study in nondiabetic hypertensive adults with chronic kidney disease and proteinuria, aliskiren plus angiotensin receptor blocker (ARB) therapy reduced proteinuria and lessened GFR decline compared with ARB monotherapy over a follow-up period of 6 months [5].

3) Adult:

a) In a retrospective study in nondiabetic hypertensive adults with chronic kidney disease and proteinuria, aliskiren plus angiotensin receptor blocker (ARB) therapy reduced proteinuria and lessened GFR decline compared with ARB monotherapy over a follow-up period of 6 months. Patients taking ARB therapy for longer than 90 days and who had an estimated GFR of 15 mL/min/1.73m(2) or higher and a spot urinary protein-to-creatinine ratio between 300 mg/g and 3500 mg/g were eligible. Some patients received add-on therapy with aliskiren for at least 90 days and were included in the analysis (n=57) and compared with the ARB monotherapy group (n=132). In both treatment groups, most patients took losartan 160 mg (78.9%) and the remaining took irbesartan 300 mg daily; the aliskiren dose for add-on therapy was 150 mg once daily. Compared with baseline, aliskiren plus ARB therapy reduced the mean urinary protein-to-creatinine ratio by 26% (ranging from 15% to 37% according to the 95% CI); there was no significant change in the amount of urine protein for the ARB monotherapy group. The decline of estimated GFR was significantly slower in the aliskiren add-on group (-2.1 mL/min) compared with the ARB monotherapy group (-4 mL/min). The proteinuria-reducing effect of aliskiren was more prominent in males, in patients with GFR less than 60 mL/min, and in patients with heavier proteinuria [5].

Diabetic nephropathy - Hypertension

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Evidence (Monotherapy)

Aliskiren as monotherapy in diabetic kidney disease is supported by little evidence from preclinical and early prospective trials, but antihypertensive and proteinuria-reducing effects

have been shown as greater than that achieved with placebo. Benefits are not superior to use of ACE inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs); however, in cases of severe allergic reaction or other contraindications to ACEIs and ARBs, use of aliskiren monotherapy may be considered [1].

Albuminuria was significantly reduced with aliskiren monotherapy compared with placebo in patients with type 2 diabetes, hypertension, and a mean baseline urinary albumin excretion rate of 275 mg/day (crossover study; N=26). Aliskiren monotherapy was no more effective than irbesartan monotherapy (albuminuria reduction, 48% vs 58%). GFR declined significantly compared with placebo in both groups [2].

Evidence (Combination Therapy)

The addition of aliskiren to treatment with an ACE inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes at high risk of fatal and nonfatal CV and renal events did not improve cardiovascular or renal outcomes, and this treatment was associated with a significantly increased risk of cardiac arrest with resuscitation (ALTITUDE; N=8561) [4].

Dose Adjustments

Adult Dosage

Normal Dosage

Oral route

Chronic kidney disease, Nondiabetic

a) Dose: 150 mg orally once daily [5]

Diabetic nephropathy - Hypertension

a) Off-label dosage: 150 [1][2][3] or 300 mg orally daily [4][2][3]

Hypertension

a) Initial dosage: 150 mg orally once daily; take consistently with regard to meals [6].

b) Titration: The dose may be increased to 300 mg once daily if the blood pressure is not adequately controlled. While doses above 300 mg did not result in increased blood pressure response, they increased the rate of diarrhea in clinical trials [6].

Dosage in Renal Failure

A) No adjustments are necessary; however, safety and effectiveness have not been established in patients with a CrCl less than 30 mL/min [6].

Dosage in Hepatic Insufficiency

A) Mild to severe impairment: No initial adjustments are necessary [6].

Dosage in Geriatric Patients

A) No initial dosage adjustments are necessary [15].

Dosage Adjustment During Dialysis

A) Hemodialysis

1) ESRD: No dosage adjustment is necessary [6].

Pediatric Dosage

Normal Dosage

Oral route

Hypertension

a) 6 to 17 Years and 20 to 50 kg

1) Initial dosage: 75 mg orally once daily; take consistently with regard to meals

[6].

2) Maximum dosage: 150 mg once daily [6]

b) 6 to 17 Years and 50 kg or Greater

1) Initial dosage: 150 mg orally once daily. Take consistently with regard to meals [6].

2) Titration: The dose may be increased to 300 mg once daily if the blood pressure is not adequately controlled. While doses above 300 mg did not result in increased blood pressure response, they increased the rate of diarrhea in clinical trials [6].

Dosage in Renal Failure

A) No adjustments are necessary; however, no data is available in pediatric patients with a GFR less than 30 mL/min/1.73m(2) [6].

Dosage in Hepatic Insufficiency

A) Mild to severe impairment: No initial adjustments are necessary [6].

Dosage Adjustment During Dialysis

A) Hemodialysis

1) ESRD: No dosage adjustment is necessary [6].

Administration

A) Preparation

1) Oral route

a) Administration

1) As high-fat meals can significantly decrease absorption, aliskiren should be taken consistently with regard to meals; high-fat meals reduce absorption significantly [6].

2) Oral pellets: Do not swallow the dispensing capsule containing the oral pellets. Do not empty contents of pellet directly into mouth and do not crush or chew the pellets. Take oral pellets by emptying capsule contents into a spoon and then administering by mouth, followed with milk (dairy or soy-based) or water immediately without crushing or chewing. Alternatively, oral pellets may be taken by mixing capsule contents with 1 teaspoon of one of the following dosing vehicles: milk- or soy-based vanilla pudding, milk- or soy-based vanilla ice cream, dairy or soy-based milk, or water. Other dosing vehicles are not recommended. More or less dosing vehicle may be used, if desired [6].

B) Oral route

1) Pellet/Tablet

a) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from moisture [6].

Comparative Efficacy

Aliskiren/Valsartan

Hypertension

a) In an 8-week (wk), multicenter, randomized, double-blind, active-control study (n=641), the addition of hydrochlorothiazide to aliskiren/valsartan therapy significantly reduced blood pressure measurements from baseline compared with the addition of hydrochlorothiazide to aliskiren or valsartan in patients with mild to moderate essential hypertension not controlled on hydrochlorothiazide alone. Following a 4-wk single-blind, hydrochlorothiazide run-in period (12.5 milligrams (mg) for 1 wk then 25 mg for 3 wk), patients (mean age, 53.2 years) with a diastolic blood pressure (DBP) of 95 millimeters of mercury (mmHg) or greater were randomized to receive 150 mg aliskiren/160 mg valsartan/25 mg hydrochlorothiazide (triple combination arm; n=168), 150 mg aliskiren/25 mg hydrochlorothiazide (n=166), 160 mg valsartan/25 mg hydrochlorothiazide (n=155), or hydrochlorothiazide 25 mg alone (n=152) once daily. The treatment dose was increased after 4 wk in the 3 hydrochlorothiazide combination arms to 300 mg aliskiren/320 mg valsartan/25 mg hydrochlorothiazide, 300 mg

aliskiren/25 mg hydrochlorothiazide, and 320 mg valsartan/25 mg hydrochlorothiazide for an additional 4 wk; however, the dosage in the hydrochlorothiazide alone arm remained at 25 mg/day for the entire 8 wk study period. At the wk 8 endpoint evaluation, DBP (primary endpoint) and systolic blood pressure (SBP) values were significantly lower from baseline in patients in the triple combination arm compared with the aliskiren/hydrochlorothiazide and valsartan/hydrochlorothiazide arms; additionally, DBP and SBP reductions were significantly improved in the 3 hydrochlorothiazide combination arms compared with the hydrochlorothiazide alone arm (see Table). Significantly more patients (p less than 0.001) in the triple combination arm (66.67%) had a SBP/DBP less than 140/90 mmHg after 8 wk compared with the aliskiren/hydrochlorothiazide (40.85%), valsartan/hydrochlorothiazide (48.7%), or hydrochlorothiazide alone (20.53%) arms. Serious adverse effects occurred in 0%, 1.8%, 3.3%, and 0.7% of patients in the triple combination, aliskiren/hydrochlorothiazide, valsartan/hydrochlorothiazide, and hydrochlorothiazide alone arms, respectively. A serum potassium level greater than 5.5 millimoles/liter was reported in one patient treated in the triple combination arm [56].

Blood Pressure Measurements	Aliskiren/ Valsartan/ Hydrochlorothiazide (n=168)	Aliskiren/ Hydrochlorothiazide (n=164)	Valsartan/ Hydrochlorothiazide (n=154)	Hydrochlorothiazide (n=152)
Diastolic Blood Pressure (DBP) (Primary Endpoint)				
Mean Baseline DBP (mmHg)	99.2 +/- 3.7	99.3 +/- 4.1	99.9 +/- 3.97	99.9 +/- 4.33
Mean Change at Endpoint (mmHg +/- SE)	-16 +/- 0.67	-14 +/- 0.7	-11 +/- 0.67	-6 +/- 0.7
p-value vs Hydrochlorothiazide	less than 0.001	less than 0.001	less than 0.001	---
p-value vs Aliskiren /Hydrochlorothiazide	less than 0.001	---	---	
p-value vs Valsartan/Hydrochlorothiazide	less than 0.001	---	---	
Systolic Blood Pressure (SBP)				
Mean Baseline DBP (mmHg)	152.7 +/- 11.64	153.3 +/- 12.68	156.7 +/- 12.49	154.1 +/- 12.61
Mean Change at Endpoint (mmHg +/- SE)	-22 +/- 1.07	-18+/- 1.12	-15 +/- 1.08	-6 +/- 1.12
p-value vs Hydrochlorothiazide	less than 0.001	less than 0.001	less than 0.001	---
p-value vs Aliskiren/Hydrochlorothiazide	less than 0.001	---	---	
p-value vs Valsartan/Hydrochlorothiazide	less than 0.011	---	---	
mmHg, millimeters of mercury; SE, standard error of the mean				

b) Treatment with aliskiren/valsartan significantly reduced blood pressure measurements from baseline compared with aliskiren or valsartan monotherapy or placebo in a subgroup of patients with stage 2 hypertension in a post-hoc analysis (n=581). Following a 1- to 2-week (wk) washout period and a 3- to 4-wk single-blind, placebo run-in period, patients with a mean sitting systolic blood pressure (SBP) of 160 millimeters of mercury (mmHg) or greater were randomized to receive aliskiren 150 milligrams (mg) (n=138), valsartan 160 mg (n=152), 150 mg aliskiren/160 mg valsartan (combination therapy; n=134), or placebo (n=157) once daily for 4 wk. The treatment dose was doubled after 4 wk to aliskiren 300 mg, valsartan 320 mg, and 300 mg aliskiren/320 mg valsartan for an additional 4 wk. At the study endpoint (defined as the blood pressure value at wk 8 or at the last post baseline measurement), DBP (primary endpoint) and SBP values were significantly lower from baseline in patients in the aliskiren 300 mg, valsartan 320 mg, and combination arm compared with placebo, and in the combination arm compared with the aliskiren 300 mg or valsartan 320 mg arms (see Table). Additionally, significantly more patients in the combination arm (29.8%) had a SBP/DBP less than 140/90 mmHg at endpoint compared with the aliskiren 300 mg (19%; p=0.044), valsartan 320 mg (13.8%; p less than 0.001), or placebo (8.9%; p less than 0.0001) arms. Serious adverse effects occurred at a similar rate among all study arms (aliskiren arm, 2%; valsartan arm, 1%; combination arm, 0.7%; placebo arm, 1%). Serum potassium levels greater than 5.5 millimoles/liter were reported in 1.5%, 3.4%, 4%, and 3.3% of patients in the aliskiren, valsartan, combination, and placebo arms, respectively [57].

Blood Pressure Measurements	Aliskiren 300 mg (n=137)	Valsartan 320 mg (n=152)	Aliskiren 300 mg/ Valsartan 320 mg (n=131)	Placebo (n=157)

Diastolic Blood Pressure (DBP) (Primary Endpoint)				
Baseline DBP (mmHg)	101.9	102.1	101.9	102.2
Mean Change at Endpoint (mmHg)	-8.9	-8.3	-11.4	-3.7
p-value vs Placebo	less than 0.0001	less than 0.0001	less than 0.0001	---
p-value vs Aliskiren 300 mg	---	---	0.0198	
p-value vs Valsartan 320 mg	---	---	0.0034	
Systolic Blood Pressure (SBP)				
Baseline SBP (mmHg)	167.3	168.5	167.3	168.3
Mean Change at Endpoint	-17.3	-15.5	-22.5	-7.9
p-value vs Placebo	less than 0.0001	less than 0.0001	less than 0.0001	---
p-value vs Aliskiren 300 mg	---	---	0.0059	
p-value vs Valsartan 320 mg	---	---	0.0001	
mmHg, millimeters of mercury				

Atenolol