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Renin Inhibitors (Tekturna[®], Tekturna HCT[®]) Step Therapy Criteria

Brand	Generic	Dosage Form
Tekturna [®]	aliskiren	oral tablets
Tekturna HCT [®]	aliskiren/hydrochlorothiazide	oral tablets

FDA-APPROVED INDICATIONS^{1,2}

Tekturna[®]

Tekturna[®] (aliskiren) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. Use with maximal doses of ACE inhibitors has not been adequately studied.

Tekturna HCT[®]

Tekturna HCT[®] (aliskiren/hydrochlorothiazide) is indicated for the treatment of hypertension.

Both aliskiren and hydrochlorothiazide are associated with dose-dependent and dose-independent adverse effects. Patients treated with Tekturna HCT may experience any or all of these adverse effects. For dose-dependent adverse effects, using a strength of Tekturna HCT with a lower dose of the component suspected of causing the adverse effect may produce better tolerability.

A patient whose blood pressure is not adequately controlled with aliskiren alone or hydrochlorothiazide alone may be switched to combination therapy with Tekturna HCT. A patient whose blood pressure is controlled with hydrochlorothiazide alone but who experiences hypokalemia may be switched to combination therapy with Tekturna HCT. A patient who experiences dose-limiting adverse reactions on either component alone may be switched to Tekturna HCT containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions.

Tekturna HCT may be substituted for the titrated components.

This fixed dose combination is not indicated for initial therapy.

RATIONALE FOR SELECTING RENIN INHIBITORS (TEKTURNA, TEKTURNA HCT) FOR STEP THERAPY

The intent of the Renin Inhibitors (Tekturna, Tekturna HCT) Step Therapy criteria is to promote the use of cost-effective generic angiotensin converting enzyme inhibitors (ACEIs), generic ACEI/diuretic combinations, angiotensin receptor blockers (ARBs), or ARB/diuretic combinations before the renin inhibitor Tekturna (aliskiren) or Tekturna HCT (aliskiren/hydrochlorothiazide). Unlike ACEIs and ARBs, which have data supporting their use in other conditions (e.g., heart failure, diabetes, etc.), and have been shown to improve clinical outcomes, published data for aliskiren so far has focused only on the treatment of hypertension.

Inhibition of the renin-angiotensin system (RAS) has been found to be an effective intervention in the treatment of cardiovascular and renal disorders; many antihypertensive agents target the RAS, including ACEIs and ARBs. The renin system can be inhibited at various points to control renal and

cardiovascular effects. Beta blockers reduce the release of renin from the juxtaglomerular apparatus, thereby lowering blood pressure. ACEIs reduce the conversion of angiotensin I to angiotensin II, and also inhibit the inactivation of bradykinin and substance P, which results in some of the side effects of ACEIs (e.g., cough, angioedema). ARBs specifically block interaction of angiotensin II with the AT1 receptor. Both ACEIs and ARBs result in increased levels of plasma renin activity (PRA). Renin inhibitors such as aliskiren block the activity of renin directly at its origin.³ Aliskiren decreases PRA and inhibits conversion of angiotensinogen to angiotensin I. The clinical implications of differences in effect on PRA are not known. Whether aliskiren affects other RAS components is not known.^{1,3}

Aliskiren was evaluated in six randomized, double-blind, placebo-controlled, 8 week clinical trials in patients with mild to moderate hypertension; five of these trials have been published.^{1,4-8} These studies included about 2,730 patients on aliskiren 75 to 600 mg, and 1,231 patients on placebo (total of 3,961 patients). Their primary endpoint was change from baseline in seated trough cuff diastolic blood pressure (DBP). Some trials evaluated active control arms, and/or combinations with another antihypertensive. In these studies, there was a dose-related increase in response with reasonable effects observed at 150 to 300 mg; there was no clear further increase in effect with 600 mg. About 85% to 90% of the blood pressure lowering effect was observed within 2 weeks of treatment.¹

As monotherapy, aliskiren 150 mg and 300 mg lowered trough DBP from baseline (Least square mean (LSM) -9.3 and -11.8 mm Hg respectively, versus placebo -6.3 mm Hg); and systolic blood pressure (SBP) (LSM -11.4 and -15.8 mm Hg respectively, versus placebo -5.3; p<0.001 versus placebo for all). Effects of aliskiren 150 mg were comparable to irbesartan 150 mg (LSM reductions in DBP and SBP from baseline -8.9 and -12.5 mm Hg, respectively). In open-label continuations of aliskiren for up to one year, a persistent blood pressure lowering effect was shown by a randomized withdrawal study (patients randomized to continued drug or placebo), which showed a statistically significant difference between patients kept on aliskiren and those randomized to placebo. With cessation of treatment, blood pressure gradually returned toward baseline levels over a period of several weeks. There was no evidence of rebound hypertension after abrupt cessation of therapy. Aliskiren lowered blood pressure in all demographic subgroups, although Black patients tended to have smaller reductions than Caucasians and Asians, as has been seen with ACEIs and ARBs.¹

In a study evaluating aliskiren and valsartan, alone and in combination, monotherapy with either drug lowered DBP and SBP versus placebo, and the combination was more effective than either monotherapy (p<0.0001 for all comparisons). LSM differences in change from baseline versus placebo: aliskiren -8.40 mm Hg, valsartan -8.20 mm Hg, aliskiren/valsartan -12.64 mm Hg.⁶

In all clinical trials including over 6,200 patients, more than 2,700 patients were exposed to combinations of aliskiren and hydrochlorothiazide (HCTZ). The safety and efficacy of Tekturna HCT were evaluated in patients with mild-to-moderate hypertension in an 8-week, randomized, double-blind, placebo-controlled, parallel-group, 15-arm factorial trial (n=2,762). Patients were randomized to receive various combinations of aliskiren (75 mg to 300 mg) plus HCTZ (6.25 mg to 25 mg) once daily (without titrating up from monotherapy) and followed for blood pressure response. The combination of aliskiren and HCTZ resulted in additive placebo-adjusted decreases in systolic and diastolic blood pressure at trough of 10-14/5-7 mmHg at doses of 150-300 mg/12.5-25 mg, compared to 5-8/2-3 mmHg for aliskiren 150 mg to 300 mg and 6-7/2-3 mmHg for HCTZ 12.5 to 25 mg, alone. Blood pressure reductions with the combinations were greater than the reductions with the monotherapies as shown in the table below.²

Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure in Combination with HCTZ²

Aliskiren, mg	Placebo mean change	Hydrochlorothiazide, mg			
		0	6.25	12.5	25
0	7.5/6.9	-	3.5/2.1	6.4/3.2	6.8/2.4
75	-	1.9/1.8	6.8/3.8	8.2/4.2	9.8/4.5
150	-	4.8/2	7.8/3.4	10.1/5	12/5.7
300	-	8.3/3.3	-	12.3/7	13.7/7.3

Aliskiren has not been studied when added to maximal doses of ACEIs to determine whether aliskiren produces additional blood pressure reduction with a maximal dose of an ACEI. Aliskiren 150 mg provided additional blood pressure reduction when given with amlodipine 5 mg in one study, but the combination was not statistically significantly better than amlodipine 10 mg.¹

The overall adverse effect profile for aliskiren was considered by the FDA to be acceptable for an antihypertensive. While diarrhea was not a substantial problem leading to discontinuations at the proposed to be marketed doses, its incidence is increased about two-fold at the highest proposed dose (300 mg) in the general population and may also be increased two-fold at the lowest proposed dose (150 mg) in some subgroups (e.g., women, elderly). Aliskiren shares adverse effects common to other RAS inhibitors: increases in serum potassium and slight/transient decreases in renal function. Cough rates were slightly increased with aliskiren vs. placebo; however, rates were lower (one half to one third) compared to ACEIs. There is currently no clinical experience with use of aliskiren in pregnant women; its labeling does contain similar pregnancy warnings to the ACEIs and ARBs.⁹

Guidelines for treatment of hypertension in the United States, the Joint National Committee (JNC-7, 2003) recommend thiazide diuretics as initial drug treatment for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes. Based on beneficial outcomes in clinical trials, patients with certain high risk concomitant conditions (e.g., heart failure, diabetes, chronic kidney disease) are considered to have compelling indications for initial use of antihypertensive drugs that inhibit the RAS (ACEIs, ARBs). Black patients are known to have reduced blood pressure responses to monotherapy with ACEIs or ARBs compared with diuretics or calcium channel blockers.¹⁰

In the United Kingdom (National Institute for Clinical Excellence: NICE, 2006) hypertension guidelines recommend the following pharmacotherapy for treatment of hypertension.¹¹ In hypertensive patients aged ≥ 55 or black patients (African or Caribbean descent) of any age, the first choice for initial therapy should be either a calcium channel blocker or a thiazide diuretic. In hypertensive patients of age < 55 , the first choice for initial therapy should be an ACEI (or ARB if an ACEI is not tolerated). If blood pressure remains uncontrolled with the first drug, second step therapy is an ACEI plus calcium channel blocker or ACEI plus thiazide diuretic.¹¹ Both guidelines state that many patients with hypertension will require more than one drug to control blood pressure.¹¹

Additional hypertension guidelines from the American Diabetes Association,¹² the British Hypertension Society,¹³ and the European Society of Hypertension/European Society of Cardiology (ESH/ESC)¹⁴ recommend ACEIs and ARBs as medications whose benefits have been shown in placebo-controlled trials. All current guidelines on treatment of hypertension were written prior to the approval of aliskiren.¹⁰⁻¹⁴

The use of ACEIs and ARBs for indications other than hypertension is supported by guidelines for treatment of heart failure, left ventricular dysfunction, post-myocardial infarction, coronary artery disease, diabetic nephropathy and renal disease.¹⁵⁻²¹ ACEIs are considered first line treatment for hypertension, HF, and for renal protection in patients with and without diabetes. ARBs should be used only after a patient has become intolerant to the ACEI due to cough or angioedema.²²⁻²⁴ Available evidence and current guidelines do not suggest ARBs have a preferred role over ACEIs in the treatment of hypertension, heart failure, or nephropathy. When inhibition of the renin-angiotensin system is indicated, ACEIs or ACEI/ diuretics should generally be preferred over ARBs; ARB use should be limited to patients with a documented failure, allergy, contraindication, or intolerance to an ACEI.

Because it is such a new medication on the market, aliskiren is not included in any of these guidelines currently. Therefore, the *PA Criteria for Approval* for Tekturna (aliskiren) and Tekturna HCT (aliskiren/hydrochlorothiazide) will require that patients try and fail an ACEI, ACEI/diuretic combination, an ARB, or ARB/diuretic combination prior to administration of Tekturna or Tekturna HCT, unless the patient has an allergy, intolerance or contraindication to the ACEI or ARB products.

Step Therapy Electronic Edit

The intent of the initial step therapy edit is to electronically identify patients and automatically pay for drug claims for the renin inhibitor Tekturna (aliskiren) or Tekturna HCT (aliskiren/ hydrochlorothiazide) if there is a prior medication history for the drug aliskiren in the previous 90 days. Approval of this medication if previous use is identified assures no disruption of therapy for those patients already stabilized on the medication. The 90-day search period was chosen to capture the most current therapy.

For patients initiating therapy with the renin inhibitor Tekturna, the step therapy edit will automatically pay if the patient has a medication history of a generic ACEI, generic ACEI/diuretic combination, ARB, or ARB/diuretic combination in the previous 90 days. Nine of the ten ACEIs are available as generic agents. ARBs are not preferred over ACEIs but ARBs are an alternative for patients who have had a documented failure, allergy, contraindication, or intolerance to ACEIs.

Prior Authorization (PA) Criteria for Approval

The intent of the prior authorization criteria is to provide a manual review process for claims that do not meet the electronic edit criteria and are not automatically paid. Claims for the renin inhibitor Tekturna will be approved if there is a history of use of the identical agent OR if the patient has tried a generic ACEI, ACEI/diuretic, an ARB, or ARB/diuretic combination and discontinued due to failure or has allergy, contraindication, or intolerance to the ACEI or ARB products.

INITIAL AUTOMATIC STEP THERAPY EDIT FUNCTIONALITY

The overall process for step therapy requires that another drug or drugs be tried in a designated time period before the claim drug. The patient must have evidence of the applicable drug-specific edit(s) in the patient's prescription drug history for the automatic payment of the submitted claim. If the patient does not meet the step edit criteria, then the system will reject with the message indicating that prior authorization (PA) is necessary. The PA criteria for approval would then be applied to requests submitted by the patients' practitioner for evaluation.

Prescriptions written for the renin inhibitor Tekturna or Tekturna HCT will automatically pay if there is a history of Tekturna (GPI 3617*****) or Tekturna HCT (GPI 36996002*****) found in the patient's medication history within the past 90 days. The edit will allow for automatic payment of a new claim if the history renin inhibitor is Tekturna and the new claim is for Tekturna HCT. If the history drug is Tekturna HCT and the new claim is Tekturna, the claim will also automatically pay. New claims for Tekturna or Tekturna HCT will automatically pay if the patient's medication history contains evidence of a generic ACEI or generic ACEI/diuretic (GPI 3610***** or GPI 36991802*****, with multi-source code Y) or an ARB or ARB/diuretic (GPI 3615***** or GPI 36994002*****) within the previous 90-day look-back period. If these claims are not found, a Point of Sale Message will be returned to the pharmacy stating that step therapy criteria was not met and that a Prior Authorization (PA) approval is necessary.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Renin Inhibitors (Tekturna, Tekturna HCT)

Initial and Renewal Evaluation

1. Is the patient currently being treated with and stable on Tekturna or Tekturna HCT?
If yes, approve for 12 months. If no, continue to 2.
2. Has the patient previously tried and failed therapy with a generic ACEI, generic ACEI/diuretic, ARB or ARB/diuretic?
If yes, approve for 12 months. If no, continue to 3.
3. Does the patient have an allergy, contraindication, or intolerance to an ACEI, ACEI/diuretic, ARB, or ARB/diuretic?
If yes, approve for 12 months. If no, deny.

CONCLUSION

Step therapy electronic edits are designed to identify specific criteria in a patient's medication history and allow payment of claims that meet the criteria. The renin inhibitor Tekturna or Tekturna HCT is automatically paid if the patient's medication history contains at least one claim for the identical product, or if there is a history of use of an ACEI, an ACEI/diuretic combination, an ARB, or an ARB/diuretic combination. If the patient's medication history does not contain the information specified in the edit the prior authorization criteria for the drug claim is applied as a member-specific review process. In this review, the prescribing physician provides patient-specific information to be taken into consideration by the reviewing physician. The renin inhibitor Tekturna or Tekturna HCT will be covered if manual review shows that the member has previously received a generic ACEI, ACEI/diuretic combination, ARB, or ARB/diuretic combination, or has a contraindication, allergy, or intolerance to ACEIs or ARBs.

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Document History

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