Management of hypertension with fixed-dose triple-combination treatments

Benjamin J. Epstein, Niren K. Shah and Nancy L. Borja-Hart

Abstract: The objective of this review is to evaluate the role of fixed-dose triple-combination therapy for the management of hypertension. An assessment of clinical trials showed that half the patients with hypertension have uncontrolled blood pressure (BP), with underlying factors including therapeutic inertia and poor patient adherence. Many patients will require three antihypertensive agents to achieve BP goals, and current guidelines recommend combining drugs with complementary mechanisms of action. Three single-pill triple-combination treatments are available and each includes an agent affecting the renin-angiotensin-aldosterone pathway [either a direct renin inhibitor or an angiotensin II receptor blocker] in combination with a calcium channel blocker and diuretic. These triple-combination therapies consistently demonstrated significantly greater BP reduction relative to the component dual combinations, with BP reductions documented across a range of patient populations. Triple-combination treatments were well tolerated in all clinical trials reviewed. The use of single-pill, triple-combination antihypertensive therapy has been shown to be an effective, well-tolerated, and convenient treatment strategy that can help patients achieve BP control.

Keywords: aliskiren, amlodipine, antihypertensive agents, drug combinations, fixed-dose triple-combination therapy, hydrochlorothiazide, hypertension, olmesartan, valsartan

Introduction

Uncontrolled blood pressure (BP) remains a major healthcare issue and individuals with high BP are at an increased risk of cardiovascular disease (CVD) morbidity and mortality [Egan et al. 2010; Heidenreich et al. 2011]. Data from the National Health and Nutrition Examination Survey 2007–2010 showed that an estimated 77.9 million adults ≥ 20 years of age have hypertension; of those with hypertension, 81.5% were aware of their condition, 74.9% were under current treatment, 52.5% had their BP controlled, and 47.5% did not have their BP controlled [Go et al. 2013]. The American Heart Association has forecasted that the economic burden of CVD attributable to hypertension will rise to approximately US$200 billion annually by 2030 [Heidenreich et al. 2011].

Effective BP reduction has been associated with reductions in the risk of cardiovascular and/or cerebrovascular events and related morbidity and mortality across a variety of patient populations [Lewington et al. 2002; Mancia et al. 2009; Staessen et al. 2005; Turnbull, 2003]. In fact, given the well-established benefits of BP control for CVD outcomes, the US Food and Drug Administration (FDA) has recently issued an industry guidance regarding antihypertensive drugs and recommends the following standardized language for the labeling of any such product, regardless of whether the antihypertensive agent has demonstrated CVD outcomes: ‘Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions’ [FDA, 2011]. Furthermore, clinical trials such as the Valsartan Antihypertensive Long-term Use Evaluation (VALUE), Systolic Hypertension in Europe (Syst-Eur), and Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) have shown that earlier diagnosis and treatment of hypertension can improve outcomes such as myocardial infarction, stroke, and cardiac morbidity and mortality [Jamerson et al. 2007; Julius et al. 2004; Staessen et al. 2004].

The fact that multiple antihypertensive therapies are often required to achieve BP control has been

Keywords: aliskiren, amlodipine, antihypertensive agents, drug combinations, fixed-dose triple-combination therapy, hydrochlorothiazide, hypertension, olmesartan, valsartan
consistently established by numerous clinical trials including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the International Verapamil-Trandolapril Study (INVEST), the Study on Cognition and Prognosis in the Elderly (SCOPE), the Hypertension Optimal Treatment (HOT) study, the Modification of Diet in Renal Disease (MDRD), and the African American Study of Kidney Disease and Hypertension (AASK) [Cushman et al. 2002; Hansson et al. 1998; Jamerson, 2003; Klahr et al. 1994; Lithell et al. 2003; Pepine et al. 2003; Wright et al. 2002]. Thus, it is well accepted that the majority of patients with hypertension require combination therapy and, based on cumulative data from clinical trials, it has been estimated that at least 25% of patients will require triple-combination therapy to achieve BP control [Gradman, 2010].

A rationale approach to combination therapy in hypertension is the selection of antihypertensive drugs that have complementary mechanisms of action, for example, combining an agent targeting the renin-angiotensin-aldosterone system (RAAS) with a diuretic and a calcium channel blocker (CCB) [Mancia et al. 2009]. Such triple-combination treatments have demonstrated greater efficacy compared with the component dual combinations, as evidenced by greater proportions of patients on triple-combination therapy achieving BP control after only 2 weeks at the highest dose [Calhoun et al. 2009b; Oparil et al. 2010]. The focus of this review is to evaluate the role of fixed-dose triple-combination therapy in hypertension management.

Hypertension guidelines

In order to achieve BP control, current guidelines recommend stepwise treatment regimens, typically with more than one antihypertensive agent [Chobanian et al. 2003; Gradman et al. 2010; Mancia et al. 2009; NICE, 2011; Rosendorff et al. 2007; Whitworth, 2003]. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) states that when BP is >20/10 mmHg above goal, consideration should be given to initiating therapy with two agents [Chobanian et al. 2003]. Similarly, the International Society on Hypertension in Blacks recommends the use of combination therapy for patients with systolic BP (SBP) > 15 mmHg above goal and diastolic BP (DBP) > 10 mmHg above goal [Flack et al. 2010]. The practicality of initiating treatment with combination therapy was demonstrated by the Simplified Intervention to Control Hypertension (STITCH) study. The analyses were based on data from 2104 patients with uncontrolled hypertension, of whom 49% were already being treated at the time of baseline assessment. In this study, a simple step-care-based algorithm featuring a low-dose, fixed-dose combination regimen for initial treatment was readily implemented in family-practice settings and resulted in better BP control compared with more conventional guideline-based management [Feldman et al. 2009]. At practices assigned to STITCH care, BP target was achieved by 64.7% compared with 52.7% for those assigned to guideline care (between-group difference: 12.1%; 95% confidence interval [CI]: 1.5–22.4%; p = 0.026) [Feldman et al. 2009]. A recent study showed that initial combination therapy was associated with a significant risk reduction of cardiovascular events and more rapid achievement of target BP was found to be the main contributor to the estimated risk reduction [Gradman et al. 2013].

Barriers to effective BP control

Therapeutic inertia

The failure of healthcare providers to increase a patient’s antihypertensive dose or change regimens to achieve BP control has been described as clinical or therapeutic inertia and represents an important provider-related barrier to BP control [Heisler et al. 2008; Hyman et al. 2000; Nesbitt, 2010; Okonofua et al. 2006]. In one study that examined this phenomenon, physicians made changes to the antihypertensive medication regimen in only 13.1% of visits for which patients had elevated BP. Estimated elevations of 13.8 mmHg in SBP and 4.5 mmHg in DBP were attributed to the presence of therapeutic inertia compared with no therapeutic inertia [Okonofua et al. 2006]. A large retrospective cohort analysis conducted in Veterans Affairs healthcare facilities (n = 38,327) found that despite documented BP elevations (68,610 BP events; mean [standard deviation] SBP 151.7 [12.3] mmHg), antihypertensive therapy was only intensified 30% of the time [Heisler et al. 2008]. Among the potential reasons that have been suggested for therapeutic inertia are physicians: (a) overestimating BP control; (b) being satisfied with BP lowering regardless of goal attainment; (c) having misperceptions regarding the use of multiple agents including complexity.
and adverse event risk [Ofili, 2006; Rose et al. 2008].

Adherence
Many factors may contribute to poor adherence. In a survey of 1432 patients with hypertension, those who self-reported difficulty in taking their antihypertensive medication (n = 407) identified the following most common underlying reasons: ‘not remembering’ (32.4%); cost (22.6%); lack of insurance (22.4%); side effects (12.5%) [Vawter et al. 2008]. Comorbidities such as depression, anxiety, or migraine were also more prevalent among patients reporting difficulty with adherence to treatment. Poor adherence to antihypertensive therapy can contribute to failure to achieve BP control and thus may be associated with a greater proportion of patients experiencing with antihypertensive medications (an 8% higher MPR was reported among treatment-naïve patients) [Sherrill et al. 2011].

Adherence to antihypertensive medications has many potential benefits for patients. For example, a population-based study of medical and pharmacy claims showed that adherence was associated with a greater proportion of patients achieving BP control [Bramley et al. 2006]. Improved adherence to antihypertensive therapy may also result in fewer CVD-related hospitalizations and a reduced number of inpatient hospital days [Lynch et al. 2009; Pittman et al. 2010; Yang et al. 2010]. A potential benefit of improved adherence among employees with hypertension is fewer days absent from work [Lynch et al. 2009]. Ultimately, better adherence may translate to fewer patients with coronary artery disease, CVD, and chronic heart failure [Bramley et al. 2010; Dragomir et al. 2010].

Overview of mechanisms of action
Antihypertensive drugs work through multiple pathways (Figure 1), and thus the combination of agents with complementary mechanisms has been put forth as a rational approach to achieving BP control [Chrysant, 2008; Eljovich and Laffer, 2009; Gradman, 2010; Sica, 2002, 2004; Wald et al. 2009]. Currently, three triple-combination therapies are available for the treatment of hypertension: Exforge HCT® (valsartan [VAL]/amlodipine [ALI]/hydrochlorothiazide [HCTZ]) (Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA); Tribenzor® (olmesartan medoxomil [OM]/AML/HCTZ) (Daiichi Sankyo, Inc., Parsippany, NJ, USA); Amturnide® (aliskiren [ALI]/AML/HCTZ) (Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) (Table 1).
Table 1. Single-pill, fixed-dose, triple-combination therapies for hypertension: indication and usage.*

<table>
<thead>
<tr>
<th>Components (drug classes)</th>
<th>Indication</th>
<th>Dosing</th>
<th>How supplied</th>
<th>Adverse reactions seen in ≥2% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exforge HCT</td>
<td>VAL [ARB]/AML [CCB]/HCTZ [thiazide diuretic]</td>
<td>Treatment of HTN to lower BP; not indicated for initial therapy</td>
<td>Once daily; dosage may be increased after 2 weeks; maximum dose 320/10/25 mg once daily</td>
<td>160/5/12.5 mg, 160/10/12.5 mg, 160/5/25 mg, 160/10/25 mg, 320/10/25 mg Bottles of 30 or 90</td>
</tr>
<tr>
<td>Tribenzor OM HCTZ</td>
<td>OM [ARB]/AML [CCB]/HCTZ [thiazide diuretic]</td>
<td>Treatment of HTN to lower BP; not indicated for initial therapy</td>
<td>Once daily; dosage may be increased after 2 weeks; maximum dose 40/10/25 mg once daily</td>
<td>20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, 40/10/25 mg Bottles of 30 or 90, or 10 blisters of 10</td>
</tr>
<tr>
<td>Amturnide ALI HCTZ</td>
<td>ALI [DRI]/AML [CCB]/HCTZ [thiazide diuretic]</td>
<td>Treatment of HTN to lower BP; not indicated for initial therapy</td>
<td>Once daily; dosage may be increased after 2 weeks; maximum dose 300/10/25 mg once daily</td>
<td>150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg, 300/10/25 mg Bottles of 30 or 90, or blisters of 100</td>
</tr>
</tbody>
</table>

*For prescribing information see Novartis Pharmaceuticals Corporation [2012a, 2012c]; Daiichi Sankyo, Inc. [2012b].

ALI, aliskiren; AML, amlodipine; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DRI, direct renin inhibitor; HCTZ, hydrochlorothiazide; HTN, hypertension; OM, olmesartan; VAL, valsartan.
Each of these single-pill triple combinations contains either an angiotensin receptor blocker (ARB) or a direct renin inhibitor (DRI), combined with a CCB and a diuretic and thus capitalizes on the complementary mechanisms of action of these individual component therapies (Figure 2) [Mancia et al. 2009]. DRIs and ARBs target different aspects of the RAAS: DRIs reduce plasma-renin activity, resulting in reduced plasma levels of the potent vasoconstrictor angiotensin II (A-2), whereas ARBs directly inhibit A-2 through competitive displacement at the AT1 receptor [Barreras and Gurk-Turner, 2003; Burnier, 2001; Fogari and Zoppi, 2010]. CCBs elicit vasodilation, leading to BP reduction by binding to distinct sites at the L-type calcium channel and reducing the entry of extracellular calcium into the cell [Noll and Luscher, 1998; Richard, 2005]. This vasodilation activates both the RAAS and sympathetic nervous system and results in reflex vasoconstriction and tachycardia. However, addition of a RAAS-blocking agent attenuates the CCB-induced activation of the RAAS, resulting in additive antihypertensive efficacy [Oparil and Weber, 2009]. Thiazide diuretics have an unclear mechanism in hypertension, but are known to inhibit the renal Na⁺/Cl⁻ cotransporter effecting sodium depletion and plasma volume reduction early on; however, with a longer duration of use, reduction in total peripheral resistance is likely to contribute to BP lowering [Birkenhager, 1990; Hjemdahl, 1984; Hughes, 2004]. Diuretics initially reduce intravascular volume and activate the RAAS, leading to vasoconstriction as well as salt and water retention. In the presence of a RAAS inhibitor, this counter-regulatory response is attenuated [Gradman et al. 2010]. Diuretic-induced activation of the RAAS increases substrate levels for angiotensin-converting enzyme (ACE) inhibitors and ARBs, converting low-renin patients to high-renin patients, ensuring consistent BP lowering [Epstein, 2010]. In addition to improved BP control, certain combinations may also be associated with improved tolerability, for example, the peripheral edema that occurs with a dihydropyridine CCB can be lessened by combining the CCB with an ARB and/or a diuretic [Gradman, 2010]. The cause of the edema is believed to be arteriolar dilation, resulting in an increased pressure gradient across capillary membranes in dependent portions of the body, which RAAS blockers are thought to counteract through venodilation.

Figure 2. Complementary mechanism of combination antihypertensive therapy with an ARB or DRI, CCB, and a thiazide diuretic. ARB, angiotensin receptor blocker; AT1, angiotensin II receptor type 1; AT2, angiotensin II receptor type 2; BP, blood pressure; CCB, calcium channel blocker; DRI, direct renin inhibitor; MOA, mechanism of action; TPR, total peripheral resistance. *Exact mechanism of antihypertensive effect is not known. Reproduced with kind permission from JTE Multimedia [Oparil and Weber, 2009].
Furthermore, through the antisympathetic effects of ACE inhibitors and ARBs, RAAS inhibitors blunt the increase in heart rate that may accompany treatment with a dihydropyridine CCB [Gradman et al. 2010].

Drug interactions and pharmacokinetics

No drug interaction studies have been conducted with the three approved triple-combination treatments; however, potential drug interactions may be anticipated based on data available for the individual antihypertensive drug components (Table 2). Among the components, AML appears to be the most likely to be affected by cytochrome P450 enzymes. In particular, CYP3A4 inhibitors can increase AML concentrations, leading to increased risk of hypotension and/or edema [Pfizer Labs, 2011]. The antihypertensive effects of ALI, HCTZ, OM, and VAL may be attenuated with co-administration with nonsteroidal anti-inflammatory drugs (NSAIDs) [Lannett Company, Inc., 2007; Daiichi Sankyo, Inc., 2012a; Novartis Pharmaceuticals Corporation, 2012b, 2012d]. In addition, periodic renal monitoring is recommended in patients using NSAIDs with agents working through the RAAS pathway (ALI, OM, and VAL) [Daiichi Sankyo, Inc., 2012a; Novartis Pharmaceuticals Corporation, 2012b, 2012d].

The FDA warns of possible risks when using ALI with ACE inhibitors and ARBs in patients with diabetes or kidney (renal) impairment. These drug combinations should not be used (i.e. are contraindicated) in patients with diabetes. In addition, a new warning is being added to avoid the use of these drug combinations in patients with kidney impairment. The prescribing information for ALI-containing drugs are being updated based on preliminary data from the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) [FDA, 2012].

Secondary analyses of these data have shown that the benefits of BP lowering with triple therapy are observed early, after only 1 week of treatment with VAL 160/AML 5/HCTZ 12.5 mg, and that these early benefits are also seen in patients with severe systolic hypertension [Calhoun et al. 2009a]. More recently, the efficacy of VAL/AML/HCTZ was reported for a subgroup of patients from the pivotal study that had 24-h ambulatory BP monitoring (ABPM) at baseline and after 8 weeks of therapy [Lacourciere et al. 2011]. Reductions in ABP were greatest for patients on triple-combination treatment (p ≤ 0.01 versus dual-combination treatment), with a reduction in mean 24-h ambulatory SBP of 30.3 mmHg and DBP of 19.7 mmHg. These reductions were relatively uniform throughout the 24-h interval.

Tribenzor

The clinical efficacy and safety of OM/AML/HCTZ was evaluated in the TripleTherapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide...
## Table 2. Drug interactions and key pharmacokinetic/pharmacodynamic information for individual components of Exforge HCT, Tribenzor, and Amtureide.*

<table>
<thead>
<tr>
<th>Component</th>
<th>Drug interaction(s) $</th>
<th>Key pharmacokinetic/pharmacodynamic parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALI</td>
<td>Cyclosporine: avoid co-administration Itraconazole: avoid co-administration Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels: co-administration may lead to increases in serum potassium NSAIDs (including COX-2 inhibitors): co-administration in patients who are elderly, volume-depleted (e.g. on diuretics), or with compromised renal function may result in deterioration of renal function, including possible acute renal failure (usually reversible); monitor renal function periodically when co-administered with NSAIDs; co-administration with NSAIDs may attenuate the antihypertensive effect</td>
<td>Poorly absorbed (bioavailability about 2.5%) $C_{\text{max}}$ between 1 h and 3 h after oral administration High-fat meal reduces mean AUC by 71% and $C_{\text{max}}$ by 85% Accumulation half-life is 24 h Major enzyme responsible for metabolism is CYP3A4 (proportion of absorbed drug that is metabolized is not known) ALI does not inhibit CYP450 isoenzymes or induce CYP3A4 Excreted in urine (approximately ¼ as parent drug) Steady-state blood levels reached in about 7–8 days Reduces plasma-renin activity to a range of 50–80%; however, the clinical implications are unknown</td>
</tr>
<tr>
<td>AML</td>
<td>Simvastatin: if simvastatin is co-administered with AML, do not exceed simvastatin doses &gt; 20 mg daily Co-administration of 180 mg diltiazem daily in elderly patients with hypertension resulted in a 60% increase in AML exposure Erythromycin co-administration in healthy volunteers did not significantly change AML systemic exposure; however, strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of AML; monitor patients for symptoms of hypotension and edema when AML is co-administered with CYP3A4 inhibitors</td>
<td>Estimated absolute bioavailability: between 64% and 90% (not altered by food) $C_{\text{max}}$ between 6 h and 12 h after oral administration Extensively (about 90%) converted to inactive metabolites by hepatic metabolism Excreted in urine (10% parent compound; 60% metabolites) 93% plasma-protein bound Terminal elimination half-life about 30–50 h Steady-state plasma levels reached after 7–8 days Pharmacokinetics not significantly influenced by renal impairment</td>
</tr>
<tr>
<td>HCTZ</td>
<td>Alcohol, barbiturates, narcotics: potentiation of orthostatic hypotension Antidiabetes drugs: dosage adjustment of antidiabetes agents may be required Cholestyramine and colestipol: reduced absorption of thiazides Corticosteroids, adrenocorticotropic hormone: hypokalemia, electrolyte depletion Lithium: reduced renal clearance of lithium and high risk of lithium toxicity when used with diuretics; should not be given with diuretics NSAIDs: can reduce diuretic, natriuretic, and antihypertensive effects of diuretics</td>
<td>Diuretic effects begin within 2 h of an oral dose, peak in 4 h, and have a duration of 6–12 h Plasma half-life varies from 5.6 h to 14.8 h HCTZ is not metabolized, but rapidly eliminated by the kidney (61% of oral dose eliminated unchanged in 24 h)</td>
</tr>
<tr>
<td>OM</td>
<td>NSAIDs (including COX-2 inhibitors): co-administration in patients who are elderly, volume-depleted (e.g. on diuretics), or with compromised renal function may result in deterioration of renal function, including possible acute renal failure (usually reversible); monitor renal function periodically when co-administered with NSAIDs; co-administration with NSAIDs may attenuate the antihypertensive effect</td>
<td>OM is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract; absolute bioavailability of olmesartan is about 26% (not affected by food) $C_{\text{max}}$ (olmesartan) 1–2 h after oral administration Highly bound to plasma proteins (99%) Total plasma clearance of olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h About 35–50% of the absorbed dose is recovered in urine; remainder is eliminated in feces via bile Biphasic elimination; terminal elimination half-life of about 13 h Steady-state levels achieved within 3–5 days</td>
</tr>
</tbody>
</table>

(Continued)
in Hypertensive Patients Study (TRINITY) [Oparil et al. 2010]. This pivotal, randomized, double-blind, placebo-controlled trial evaluated OM 40/AML 10/HCTZ 25 mg versus the component dual combinations (OM 40/AML 10 mg; OM 40/HCTZ 25 mg; AML 10/HCTZ 25 mg) in patients with moderate to severe hypertension. Patient adherence was monitored by assessing the tablet count from drug packages at each visit. Adherence to study medication was similar across treatment groups, ranging from 98.0% to 98.5%. OM/AML/HCTZ reduced least squares (LS) mean SESBP by 37.1 mmHg and SEDBP by 21.8 mmHg (Table 3). This BP reduction was statistically significant compared with the dual-combination treatments (p < 0.001) at week 12. A significantly greater proportion of patients receiving triple-combination treatment achieved a BP target of <140/90 mmHg (69.9%) compared with the dual combinations at week 12 (41.1–53.4%; p < 0.001 for all comparisons). The majority of treatment-emergent adverse events observed during the study were of mild or moderate severity. Nasopharyngitis (3.5%), muscle spasms (3.1%), hypotension (1.4%), and orthostatic hypotension (0.3%) occurred more frequently in the triple-combination treatment group compared with the dual-combination treatment groups. Incidences of dizziness in the OM 40/AML 10 mg, OM 40/HCTZ 25 mg, AML 10/HCTZ 25 mg, and OM 40/AML 10/HCTZ 25 mg groups were 4.9%, 10.0%, 3.1%, and 9.9%, respectively. The incidence of peripheral edema was 1.0% in the OM 40/HCTZ 25 mg group, compared with 7.0–8.3% in the other treatment groups in which AML was a component.

A subgroup of patients from the TRINITY study had 24-h ABPM at baseline and after 12 weeks of therapy [Izzo et al. 2011]. At week 12, OM 40/AML 10/HCTZ 25 mg resulted in a greater reduction in mean 24-h SBP and DBP (30.3/18.0 mmHg) compared with the three dual-combination regimens (OM 40/AML 10 mg: 23.5/13.9, OM 40/HCTZ 25 mg: 23.9/14.5; AML 10/HCTZ 25 mg: 18.5/10.7 mmHg; all p < 0.0001).

A prespecified subgroup analysis of Black and non-Black patients in the TRINITY study demonstrated that for each of the race subgroups, LS mean BP reductions at week 12 were significantly greater for the triple combination versus the dual combinations (p ≤ 0.0001) [Chrysant, 2012]. At week 12, BP goal attainment with the triple-combination treatment was comparable for Black patients (61.5%) and non-Black patients (65.5%), and significantly greater than that seen with the dual-combination treatments. Another subgroup analysis of the TRINITY study evaluated the efficacy and safety of OM/AML/HCTZ in patients

### Table 2. [Continued]

<table>
<thead>
<tr>
<th>Component</th>
<th>Drug interaction(s) $</th>
<th>Key pharmacokinetic/pharmacodynamic parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAL</td>
<td>Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and, in heart failure patients, to increases in serum creatinine. NSAIDs (including COX-2 inhibitors): co-administration in patients who are elderly, volume-depleted (e.g. on diuretics), or with compromised renal function may result in deterioration of renal function, including possible acute renal failure (usually reversible); monitor renal function periodically when ALI is co-administered with NSAIDs; co-administration with NSAIDs may attenuate the antihypertensive effect.</td>
<td>Absolute bioavailability is about 25% C&lt;sub&gt;max&lt;/sub&gt; is 2–4 h after oral administration Food decreases AUC by about 40% and C&lt;sub&gt;max&lt;/sub&gt; by about 50% Highly bound to serum proteins (95%), mainly serum albumin Does not seem to be metabolized by CYP450 isoenzymes Following IV administration, plasma clearance is about 2 L/h and renal clearance is 0.62 L/h (about 30% of total clearance) After oral administration, primarily eliminated in feces (about 83% of dose) and urine (about 13% of dose); recovered mostly as unchanged drug (about 20% recovered as metabolites) Average elimination half-life after IV administration about 6 h</td>
</tr>
</tbody>
</table>

*For prescribing information see Lannett Company, Inc. [2007]; Pfizer Labs [2011]; Daiichi Sankyo, Inc. [2012a]; Novartis Pharmaceuticals Corporation [2012b, 2012d].

$This table includes the key or common drug interactions; this table does not include all the drug interactions for these agents.

ALI, aliskiren; AML, amlodipine; AUC, area under curve; C<sub>max</sub>, peak plasma concentration; COX-2 inhibitors, selective cyclooxygenase inhibitors; HCTZ, hydrochlorothiazide; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; OM, olmesartan; VAL, valsartan.
with hypertension and diabetes [Chrysant et al. 2012]. Regardless of diabetes status, the triple combination resulted in significantly greater reductions in SEBP relative to the component dual combinations. Of note, although the goal BP in patients with diabetes was <130/80 mmHg (10 mmHg lower than the goal in patients without diabetes), 41.1% of patients with hypertension and diabetes were able to achieve BP <130/80 mmHg with OM/AML/HCTZ compared with 10.1–16.3% of diabetic patients taking the dual combinations (all \(p\leq0.0002\)).

The 40-week open-label extension of the TRINITY study demonstrated that long-term administration of OM/AML/HCTZ was associated with BP reductions comparable to those seen during the double-blind treatment period, thus demonstrating the durable antihypertensive effect of this triple combination. At the end of the study, the mean BP decreased from 168.6/100.7 mmHg (baseline BP at randomization) to 125.0–136.8/77.8–82.5 mmHg, depending on treatment [Kereiakes et al. 2012].

**Amlturnide**

The efficacy and safety of ALI 300/AML 10/HCTZ 25 mg was compared with the component dual combinations (ALI 300/AML 10 mg; ALI 300/HCTZ 25 mg; AML 10/HCTZ 25 mg) in patients with moderate to severe hypertension [Lacourciere et al. 2012]. BP lowering achieved with the triple combination was significantly greater than with the component dual combinations. Treatment with the ALI/AML/HCTZ combination resulted in a LS mean SEBP reduction of 30.7/15.9 mmHg from baseline at week 4 and 37.9/20.6 mmHg at week 8 (\(p<0.001\) versus all dual-combination treatments) (Table 3). Clinically relevant SEBP reductions were evident within 2 weeks of treatment with the triple combination. In patients with severe hypertension (defined as SBP \(\geq\) 180 mmHg at baseline), ALI/AML/HCTZ combination therapy resulted in a BP reduction of 49.5/22.5 mmHg at week 8 (\(p<0.001\) versus all dual combinations). Most adverse events were mild or moderate, with the overall incidence comparable in the four treatment groups: 33.4% (ALI/AML), 32.3% (ALI/HCTZ), 33.6% (AML/HCTZ), and 36.2% (ALI/AML/HCTZ). Peripheral edema was the most frequently reported adverse event in this study [Lacourciere et al. 2012].

A long-term, open-label study showed that ALI 300/AML 10/HCTZ 25 mg triple-combination therapy was well tolerated and efficacious for up to 54 weeks in patients with moderate to severe hypertension [Murray et al. 2012].

---

**Table 3.** BP reductions and goal attainment for VAL/AML/HCTZ, OM/AML/HCTZ, ALI/AML/HCTZ and component dual combinations for the total cohort.*

<table>
<thead>
<tr>
<th>N</th>
<th>LS mean BP reduction from baseline (mmHg)</th>
<th>BP &lt;140/90 mm Hg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAL/AML/HCTZ 320/10/25 mg</td>
<td>39.7/24.7(^{\text{\dagger}})</td>
<td>70.8(^{\ast})</td>
</tr>
<tr>
<td>VAL/AML 320/10 mg</td>
<td>33.5/21.5</td>
<td>54.1</td>
</tr>
<tr>
<td>VAL/HCTZ 320/25 mg</td>
<td>32.0/19.7</td>
<td>48.3</td>
</tr>
<tr>
<td>AML/HCTZ 10/25 mg</td>
<td>31.5/19.5</td>
<td>44.8</td>
</tr>
<tr>
<td>OM/AML/HCTZ 40/10/25 mg</td>
<td>37.1/21.8(^{\ast})</td>
<td>69.9(^{\ast})</td>
</tr>
<tr>
<td>OM/AML 40/10 mg</td>
<td>30.0/18.0</td>
<td>52.9</td>
</tr>
<tr>
<td>OM/HCTZ 40/25 mg</td>
<td>29.7/16.9</td>
<td>53.4</td>
</tr>
<tr>
<td>AML/HCTZ 10/25 mg</td>
<td>27.5/15.1</td>
<td>41.1</td>
</tr>
<tr>
<td>ALI/AML/HCTZ 300/10/25 mg</td>
<td>37.9/20.6(^{\dagger})</td>
<td>62.3(^{\dagger})</td>
</tr>
<tr>
<td>ALI/AML 300/10 mg</td>
<td>31.4/18.0</td>
<td>41.3</td>
</tr>
<tr>
<td>ALI/HCTZ 300/25 mg</td>
<td>28.0/14.3</td>
<td>33.1</td>
</tr>
<tr>
<td>AML/HCTZ 10/25 mg</td>
<td>30.8/17.0</td>
<td>39.0</td>
</tr>
</tbody>
</table>

*Calhoun et al. [2009b]; Lacourciere et al. [2012]; Oparil et al. [2010].

\(^{\dagger}\) \(p<0.0001\), \(^{\ast}\) \(p<0.001\) versus component dual combinations.

ALI, aliskiren; AML, amlodipine; BP, blood pressure; HCTZ, hydrochlorothiazide; LS, least squares; OM, olmesartan; VAL, valsartan.
self-identified minority patients (Black, Hispanic/Latino) [Ferdinand et al. 2011]. Although the ALI/AML dual combination resulted in effective BP reductions, the triple combination resulted in greater mean BP reductions ($p < 0.0001$ for SESBP and $p = 0.0005$ for SEDBP). Differences between the groups were seen by 2 weeks of treatment.

**Potential place in therapy for single-pill triple combinations**

Single-pill triple-combination therapy may be considered in patients who have uncontrolled hypertension and are taking two separate drugs, a two-drug combination, or three separate drugs, and are experiencing adherence issues [Elijovich and Laffer, 2009; Gradman, 2010]. Even among patients who have well-controlled BP, consolidating triple free-drug therapy into a single pill offers a regimen that is more convenient and perhaps more affordable in certain circumstances. If the cost of a single-pill triple-combination therapy represents a barrier to treatment for a particular patient, healthcare providers have an important role in raising awareness of or facilitating usage of available resources such as patient assistance or reimbursement programs. Perhaps the greatest clinical benefit of single-pill combinations relative to multiple pills is the potential for improved adherence and the resulting improved control of BP [Bangalore et al. 2007; Brixner et al. 2008; Dickson and Plauschinat, 2008; Gupta et al. 2010; Yang et al. 2010; Zeng et al. 2010]. Newly available single-pill triple combinations offer patients a well-tolerated and convenient option that can improve adherence to therapy. Notably, all three currently available triple combinations have demonstrated significantly better BP lowering compared with the component dual combinations [Novartis Pharmaceuticals Corporation, 2012a; Calhoun et al. 2009b; Oparil et al. 2010].

**Acknowledgements**

Editorial support for this article was provided by Vrinda Mahajan, PharmD, of Peloton Advantage, LLC, Parsippany, NJ, USA and funded by Daiichi Sankyo, Inc, Parsippany, NJ, USA. The opinions expressed in the current article are those of the authors.

**Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Conflict of interest statement**

The authors report no conflict of interest.

**References**


