Review

Abstract: In most patients with hypertension, especially Stage 2 hypertension, adequate control of blood pressure (BP) is only achieved with combination drug therapy. When using combination therapy, antihypertensive agents with complementary mechanisms of action are recommended, for example, an angiotensin receptor blocker (ARB) in combination with hydrochlorothiazide (HCTZ), a β-blocker + HCTZ, an ACE inhibitor + HCTZ, or a calcium channel blocker + an ACE inhibitor. One such combination is olmesartan medoxomil + HCTZ, which is available as fixed-dose, single-tablet combinations for once-daily administration. In clinical trials, olmesartan medoxomil/HCTZ reduced systolic BP (SBP) and diastolic BP (DBP) to a greater extent than either component as monotherapy. A clinical study in patients with Stage 1 or 2 hypertension showed that olmesartan medoxomil/HCTZ achieved a similar mean reduction in DBP, but a significantly greater mean reduction in SBP and higher rate of BP control (<140/90 mmHg) than observed with losartan/HCTZ, at US/European-approved starting doses. In a non-inferiority trial, the antihypertensive efficacy of olmesartan medoxomil/HCTZ was comparable to that of atenolol/HCTZ. Furthermore, indirect comparisons have shown that olmesartan medoxomil/HCTZ compares favorably with other antihypertensive combination therapies, including other ARB/HCTZ combinations and amlodipine besylate/benazepril. Olmesartan medoxomil/HCTZ is generally well tolerated. In conclusion, olmesartan medoxomil/HCTZ is an effective and well-tolerated combination antihypertensive therapy that results in significant BP reductions and BP control in many patients.

Keywords: olmesartan medoxomil, hydrochlorothiazide, angiotensin II receptor blocker, hypertension

Introduction

Hypertension is a highly prevalent cardiovascular risk factor, affecting an estimated 65 million people in the United States alone (American Heart Association 2006). The control of blood pressure (BP) is important for the prevention of cardiovascular morbidity and mortality; however, as many as two-thirds of patients do not have their BP adequately controlled (Chobanian et al 2003). Treatment goals recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and international guidelines are <140/90 mmHg, or <130/80 mmHg for patients with diabetes or chronic renal disease (European Society of Hypertension 2003; Chobanian 2003; Whitworth 2003) In most patients, especially those with Stage 2 hypertension (systolic BP [SBP] ≥160 mmHg or diastolic [DBP] ≥100 mmHg), combination therapy is needed to achieve adequate control of BP, and it is generally recommended that drugs with complementary mechanisms of action should be used (Chobanian et al 2003).

Several fixed-dose combinations are now available, including β-blockers + hydrochlorothiazide (HCTZ), ACE inhibitors + HCTZ, angiotensin receptor blockers (ARBs) + HCTZ, and ACE inhibitors + calcium channel blockers. Many of these combinations are available in fixed-dose, single-tablet combinations for once-daily administration, including olmesartan medoxomil/HCTZ, which has been shown to provide greater BP control than losartan/HCTZ at US/European-approved starting doses. Further, 2016 international guidelines recommend that women ≥60 years of age should have BP targets of <140/90 mmHg, or <130/80 mmHg for patients with diabetes or chronic renal disease (European Society of Hypertension 2013; Chobanian 2013; Whitworth 2013). Olmesartan medoxomil/HCTZ is generally well tolerated, with a similar safety profile to losartan/HCTZ in clinical trials.
agents combine drugs with synergistic mechanisms of action allowing for substantially greater reductions in BP compared with component monotherapies. For example, patients are more responsive to the BP-lowering effects of ARBs and ACE inhibitors upon the addition of HCTZ. Although the mechanism(s) involved are not clearly understood, HCTZ may activate the renin-angiotensin system (RAS), making BP more dependent on angiotensin II (Kjeldsen et al. 2005). These effects on counter-regulatory processes may help to explain why the combination of an ARB or an ACE inhibitor with HCTZ reduces BP more effectively than either agent alone (Brown et al. 1990; Chrysant 1994; Benz et al. 1998; Kochar et al. 1999; Manolis et al. 2000; Chrysant et al. 2004).

Olmesartan medoxomil/HCTZ is the most recent fixed-dose ARB/HCTZ combination to be approved for the treatment of hypertension. This review will focus on the pharmacodynamics, antihypertensive efficacy, and tolerability of olmesartan medoxomil/HCTZ and how it compares with other currently available fixed-dose combinations.

**Pharmacology of olmesartan medoxomil and HCTZ**

The clinical effects of angiotensin II, including vasoconstriction, increasing intravascular volume, and hormone secretion are mediated by AT1 receptors (Burnier 2001). Olmesartan medoxomil is an AT1 receptor antagonist, demonstrating specificity for receptors in vascular tissue (Mizuno et al. 1995; Koike et al. 2001). In vitro, olmesartan medoxomil has been shown to be a competitive antagonist, displaying high affinity, slow dissociation, and a high degree of insurmountability for the AT1 receptor (Pugsley 2006). The interaction of olmesartan with the AT1 receptor is believed to occur via a two-step mechanism: the molecule first undergoes a loose “surmountable” binding followed by the formation of a tighter, “insurmountable” binding complex. The slow dissociation of olmesartan medoxomil from the AT1 receptor compares favorably with other ARBs’ dissociation, including telmisartan, and may contribute to the antihypertensive efficacy of olmesartan medoxomil in vivo (Pugsley 2006). The pressor response to exogenous angiotensin I is inhibited to a clinically relevant extent (>75%) by single doses of olmesartan medoxomil 10–40 mg, with substantial inhibition still apparent 24 hours after dosing (Brunner and Nussberger 2001).

Thiazide diuretics such as HCTZ promote sodium excretion, leading to a reduction in plasma volume and peripheral resistance (Meredith 2005). The resulting activation of the RAS means that the effect of blocking AT1 receptors and, therefore, the response to ARB therapy, is enhanced, providing a rationale for co-administration of agents from these two drug classes (Meredith 2005). Other synergistic mechanisms are thought to be involved but are not clearly understood. The increased efficacy resulting from the combination of HCTZ with an ARB does not greatly compromise the good tolerability profile of the ARB. The combination of these two agents may permit the use of lower doses of HCTZ and the ARB, which may be less likely to result in adverse events typically associated with HCTZ use.

Olmesartan medoxomil is a pro-drug that is de-esterified to its active metabolite, olmesartan, during absorption from the gastrointestinal tract (Laenis et al. 2001). Absorption is rapid, with steady-state levels reached within 5 days (Laenis et al. 2001). Importantly, the long terminal elimination half-life of 10–18 hours, coupled with minimal accumulation, allows for once-daily dosing (Laenis et al. 2001; Schwocho and Masonson 2001). Systemically available olmesartan is excreted via the kidneys and, after secretion in bile, in the feces (Laenis et al. 2001).

HCTZ is absorbed rapidly after oral administration and is eliminated unchanged in the urine (Carter et al. 2004; Sweetman 2005). It has an elimination half-life of 8–15 hours after repeated doses, and the pharmacodynamic response is sufficiently long to allow once-daily dosing (Carter et al. 2004). Clinically relevant pharmacokinetic interactions do not occur between these two agents (Kreutz et al. 2006). Given both the pharmacokinetic and the pharmacodynamic profiles of these agents, the combination of olmesartan medoxomil with HCTZ is suitable for once-daily administration in a single tablet.

**Antihypertensive efficacy of olmesartan medoxomil/HCTZ**

A number of studies have provided evidence that the combination of olmesartan medoxomil/HCTZ is an effective option for antihypertensive therapy.

**Comparison with monotherapy**

A clinical trial using a randomized, double-blind, factorial design showed that olmesartan medoxomil/HCTZ combination therapy reduced DBP and SBP to a greater extent than monotherapy with either component (Chrysant et al. 2004). In this study, hypertensive patients (n=502) with a seated DBP of 100–115 mmHg were randomized to one of 12 treatment groups for 8 weeks: olmesartan medoxomil...
(10, 20, or 40 mg/day), HCTZ monotherapy (12.5 or 25 mg/day), one of six groups of olmesartan medoxomil/HCTZ combination therapy (covering each possible dosage combination), or placebo.

A dose-dependent decrease in BP was seen across all olmesartan medoxomil/HCTZ combinations compared with the individual components, with the maximum mean reduction of 26.8/21.9 mmHg observed with the highest-dose combination, olmesartan medoxomil/HCTZ 40/25 mg/day. After 8 weeks, mean reductions in seated DBP were 13.5–21.9 mmHg with combination therapy, compared with 11.3–14.6 mmHg with olmesartan medoxomil monotherapy (10–40 mg/day), and 10.2–12.9 mmHg with HCTZ monotherapy (12.5 or 25 mg/day). All combination and monotherapy regimens reduced DBP and SBP significantly more than placebo (Chrysant et al 2004).

The proportion of patients achieving a BP response (defined as trough seated DBP <90 mmHg or a decrease from baseline of ≥10 mmHg) increased in a dose-dependent manner with each monotherapy and with combination therapy, although between-group statistical comparisons were not performed (Chrysant et al 2004). The response rate was 92.3% for olmesartan medoxomil/HCTZ 40/25 mg/day; diastolic control (trough seated DBP <90 mmHg) and systolic control (trough seated SBP <140 mmHg) were achieved in 79.5% and 87.2% of patients, respectively (Chrysant et al 2004).

Additional support for combination therapy with olmesartan medoxomil/HCTZ comes from a trial in hypertensive patients with a seated DBP of 100–115 mmHg, a seated SBP >150 mmHg, a 24-hour DBP ≥84 mmHg, and at least 30% DBP daytime readings >90 mmHg. Mean seated DBP remained ≥90 mmHg after 4 weeks of treatment with olmesartan medoxomil 20 mg/day; however, the addition of HCTZ 12.5 or 25 mg for 8 weeks significantly reduced mean 24-hour DBP (−1.9 mmHg for HCTZ 12.5 mg, p=0.0167; −3.7 mmHg for HCTZ 25 mg, p<0.0001) and SBP (−3.8 mmHg for HCTZ 12.5 mg, p=0.0018; −7.4 mmHg for HCTZ 25 mg, p<0.0001) compared with the addition of placebo (Sellin et al 2005).

**Evaluation of treatment algorithm including olmesartan medoxomil/HCTZ**

A stepwise treatment algorithm in which titration of olmesartan medoxomil is followed by the addition of increasing dosages of HCTZ is an effective option in patients with Stage 1 or Stage 2 hypertension (Neutel et al 2004, 2006).

In this open-label, multicenter study (n=210), olmesartan medoxomil 20 mg/day was initially administered for 4 weeks. Antihypertensive drug treatment was then titrated at 4-week intervals until goal BP was achieved, progressing through the following steps: titration to olmesartan medoxomil 40 mg/day, addition of HCTZ 12.5 mg/day, titration of HCTZ to 25 mg/day, addition of amlodipine besylate 5 mg/day, and then titration of amlodipine besylate to 10 mg/day (Neutel et al 2004, 2006). Endpoints included the percentage of patients who achieved the BP goal of ≤140/90 mmHg, and the more aggressive BP goal of ≤130/85 mmHg. Those patients who achieved the more aggressive BP goal at any time during the study exited the trial.

The results of this study showed that a BP goal of ≤140/90 mmHg and a more aggressive BP goal of ≤130/85 mmHg could be achieved in many patients using a combination of olmesartan medoxomil and HCTZ (Neutel et al 2004, 2006). The goal of ≤140/90 mmHg was achieved in 83% of patients after 8 weeks of dual combination therapy with olmesartan medoxomil/HCTZ (titrated to 40/25 mg/day), while the goal of ≤130/85 mmHg was attained in 69% (Neutel et al 2004). Mean BP reductions and goal attainment rates for all patients and for patients separated into those with Stage 1 or Stage 2 hypertension are shown in Figure 1. Looking specifically at the SBP goal (≤140 mmHg), 96.2% of patients with Stage 1 hypertension (mean baseline SBP of 151.1 mmHg) and 78% of those with Stage 2 hypertension (mean baseline SBP of 169.8 mmHg) achieved this goal (Neutel et al 2006). For all patients combined after 8 weeks of treatment with olmesartan medoxomil/HCTZ (titrated to 40/25 mg/day), mean BP had decreased from baseline by 29.3/16.1 mmHg, representing an incremental mean BP reduction of approximately 11.6/5.4 mmHg beyond that achieved with monotherapy. The addition of amlodipine besylate led to further decreases in BP (Neutel et al 2004).

**Comparison with other ARB/HCTZ combinations**

One direct comparison of olmesartan medoxomil/HCTZ with another ARB/HCTZ combination has been published recently. In this starting-dose, open-label comparison, olmesartan medoxomil/HCTZ and losartan/HCTZ were compared as initial therapy in patients with either newly diagnosed Stage 2 hypertension or a DBP of 90–100 mmHg despite treatment (Rump et al 2006). In this randomized, double-blind, multicenter trial, patients were treated with
starting doses of each ARB (olmesartan medoxomil 20 mg/day [n=308] or losartan 50 mg/day [n=305]) plus HCTZ 12.5 mg/day for 12 weeks. Mean BP reductions and BP control rates (<140/90 mmHg) were compared after 1, 2, 4, 8, and 12 weeks of therapy; the primary endpoint was change in DBP from baseline to 12 weeks. Olmesartan medoxomil/HCTZ and losartan/HCTZ produced similar mean reductions in DBP (–17.6 and –16.5 mmHg, respectively; Figure 2). The mean reduction in SBP was 29.3 mmHg for olmesartan medoxomil/HCTZ compared with 24.9 mmHg for losartan/HCTZ (p≤0.0003). A significantly higher percentage of olmesartan medoxomil/HCTZ recipients achieved BP control (<140/90 mmHg) at week 12 compared with losartan/HCTZ recipients (43.2% vs 32.1%, p=0.002) (Rump et al 2006).

An indirect comparison of olmesartan medoxomil/HCTZ with several other ARB/HCTZ combinations was performed in a review of randomized, double-blind, placebo-controlled factorial studies of similar design in hypertensive patients with a DBP of 95–115 mmHg (Ram 2004). At maximum US and European approved dosages, olmesartan medoxomil/HCTZ compared favorably with irbesartan/HCTZ, telmisartan/HCTZ, and valsartan/HCTZ, with each combination producing double-digit reductions (not placebo-adjusted) in both SBP and DBP (Table 1) (Ram 2004). DBP response rates (DBP<90 mmHg or a ≥10 mmHg reduction from baseline) were numerically greater with olmesartan medoxomil/HCTZ than telmisartan/HCTZ or valsartan/HCTZ (eg, 92% vs 79% vs 81%; value not reported for irbesartan) (Ram 2004).

Abbreviations: DBP, diastolic BP; HCTZ, hydrochlorothiazide; SBP, systolic BP.
For indirect comparative purposes, data from a meta-analysis (Conlin et al 2000) evaluating randomized controlled trial data of several other ARB/HCTZ combinations are presented in Table 2. All trials were in hypertensive patients with a DBP of 95–115 mmHg, assessed cuff BP, and used a similar definition of response rates (DBP <90 mmHg or a decrease from baseline of ≥10 mmHg). Combination therapy with HCTZ 12.5 mg/day plus starting doses of candesartan, irbesartan, losartan, or valsartan was associated with mean reductions in BP of 16.1–20.6/9.9–13.6 mmHg and response rates of 56–70% when administered at starting combination doses. In a trial of eprosartan/HCTZ 600/12.5 mg/day which used similar criteria as above, mean BP reductions of 9.2/10.7 mmHg and a response rate (DBP<90 mmHg or within 90–100 mmHg with a decrease of ≥10 mmHg) of 73% were reported (Sachse et al 2002). Based on these indirect comparisons, olmesartan medoxomil/HCTZ may achieve BP response rates that compare favorably with other ARB/HCTZ combinations at starting dosages (Table 2). However, direct comparative studies are required to confirm these findings.

Lastly, a study evaluating irbesartan/HCTZ in patients with Stage 1 systolic hypertension (SBP 140–159 mmHg) uncontrolled by monotherapy found that treatment with irbesartan/HCTZ 300/25 mg/day led to a mean reduction in BP of approximately 21.5/10.4 mmHg (from a mean baseline BP of 154/91 mmHg), with 69% of patients reaching the combined BP goal of <140/90 mmHg, and 77% achieving SBP goal, after 18 weeks (Neutel et al 2005). In comparison, in a trial discussed earlier, olmesartan medoxomil/HCTZ 40/25 mg/day reduced mean BP by 24.8/15.8 mmHg (from a baseline of 151.1/94.7 mmHg) in patients with Stage 1 hypertension, and by 32.7/16.3 mmHg (baseline 169.8/98.6 mmHg) in those with Stage 2 hypertension; SBP goal (≤140 mmHg) was achieved in 96.2% and 78% of these subgroups, respectively (Neutel et al 2006). Additional direct comparative studies are now needed to more accurately determine the comparative efficacy of olmesartan medoxomil/HCTZ and other ARB/HCTZ combinations.

Comparison with other antihypertensive combinations

Several clinical studies have compared the efficacy of olmesartan medoxomil/HCTZ with other antihypertensive combination therapies. For example, a study that compared olmesartan medoxomil/HCTZ with atenolol/HCTZ found that the antihypertensive efficacy of both combinations was statistically comparable (Ball et al 2001). In this double-blind, non-inferiority study, 328 patients with a mean seated DBP of 100–120 mmHg receiving HCTZ 25 mg/day were randomized to receive olmesartan medoxomil 10 mg/day or atenolol 50 mg/day in addition to the HCTZ dose for 12 weeks, with dose-doubling after 4 weeks, if necessary. Reductions in mean seated SBP and DBP (primary endpoint) were 20.4/17.3 mmHg for olmesartan medoxomil/HCTZ and 19.6/17.2 mmHg for atenolol/HCTZ. The upper limit of the one-sided confidence interval (CI) for the between-group difference for change in DBP (–0.08 mmHg; 90% CI –1.17, 1.02) was within the prespecified least squares mean limit of ≤3.5 mmHg, confirming that the efficacy of olmesartan medoxomil/HCTZ was not inferior to atenolol/HCTZ. The outcome was similar for SBP (between-group difference –0.8 mmHg, 95% CI –2.61, 1.00) (Ball et al 2001).

Amlodipine besylate/benazepril is a well-established, fixed-dose calcium channel blocker/ACE inhibitor combination antihypertensive therapy. A direct comparison
between amlodipine besylate/benazepril and olmesartan medoxomil/HCTZ has not been performed; however, an indirect comparison of data from several factorial studies (Quan et al. 2006) suggests that mean reductions in seated DBP may be quantitatively greater with olmesartan medoxomil/HCTZ 40/25 mg/day than with amlodipine besylate/benazepril 5/20 mg/day (approximately 22 vs 17 mmHg), whereas reductions in seated SBP appear similar between the combinations (approximately 27 vs 27 mmHg) (Quan et al. 2006). The studies used similar designs and enrolled patients with a baseline DBP of 100–115 mmHg. However, a head-to-head trial is needed to properly compare these combination therapies, and inclusion of the highest available dosage of amlodipine besylate/benazepril 10/20 mg (for which factorial study data were not available) would be of interest.

**Tolerability of olmesartan medoxomil/HCTZ**

Looking first at the individual components, an integrated analysis of efficacy and safety demonstrated that the adverse events profile observed with olmesartan medoxomil monotherapy is similar to that seen with placebo, with dizziness the only adverse event to occur in a significantly greater number of olmesartan medoxomil patients compared with placebo (2.8% vs 0.9%, respectively, p=0.01) (Neutel 2001). In comparison, HCTZ has been associated with metabolic disturbances and electrolyte imbalances, including hypokalemia and hyponatremia, particularly at higher doses (Sweetman 2005). Physiological processes that conserve sodium in the body, such as activation of the RAS, produce an augmentation of renal potassium excretion (Reyes 2002). Although clinical data are still lacking, it has been suggested that the inhibition of the RAS resulting from co-therapy with an ARB may reduce potassium loss, making hypokalemia less of a potential problem among patients receiving this combination (Kjeldsen et al. 2005). In addition, the tendency of HCTZ to elevate blood glucose levels and promote type 2 diabetes mellitus may be offset with the use of ARBs which have been shown to reduce the incidence of new-onset diabetes as compared with β-blocker/HCTZ therapy (Dahlof et al. 2002).

Adverse events associated with the combination of olmesartan medoxomil plus HCTZ are generally mild-to-moderate in severity (Ball et al. 2001; Chrysant et al. 2004; Neutel et al. 2004; Rump et al. 2006). Dizziness was reported by more olmesartan medoxomil/HCTZ recipients than placebo recipients in placebo-controlled trials, and was associated with the addition of HCTZ (incidence 9% for olmesartan medoxomil/HCTZ vs 2% for placebo vs 8% for HCTZ monotherapy and 1% for olmesartan medoxomil monotherapy) (Daiichi Sankyo, Inc. 2005). Upper

### Table 1

| Treatment            | Dosage (mg/day) | Mean absolute (placebo-subtracted) reduction from baseline (mmHg) | Absolute (placebo-subtracted) response rate (%) |
|----------------------|-----------------|-----------------------------------------------------------------|-----------------------------------------------|
|                      |                 | SBP                          | DBP                          |                                               |
| Irbesartan/HCTZ      | 100/12.5        | 14.9 (12.6)                  | 11.9 (8.4)                    | –                                             |
|                      | 300/25          | 23.1 (20.8)                  | 14.4 (10.9)                   | –                                             |
| Olmesartan medoxomil/HCTZ | 20/12.5         | 20.1 (16.8)                  | 16.4 (8.2)                    | 79 (41)                                       |
|                      | 20/25           | 27.1 (23.8)                  | 20.0 (11.6)                   | 89 (51)                                       |
|                      | 40/25           | 26.8 (23.5)                  | 21.9 (13.7)                   | 92 (54)                                       |
| Telmisartan/HCTZ     | 40/12.5         | 18.8 (15.9)                  | 12.6 (8.8)                    | 63 (34)                                       |
|                      | 80/12.5         | 23.9 (21.0)                  | 14.9 (11.1)                   | 79 (50)                                       |
| Valsartan/HCTZ       | 80/12.5         | 16.5 (14.6)                  | 11.8 (7.7)                    | 64 (35)                                       |
|                      | 160/25          | 22.4 (20.5)                  | 15.3 (11.2)                   | 81 (52)                                       |

*Mean change in SBP and DBP at study end (or last observation carried forward) in the intent-to-treat population, except for the irbesartan study for which data are for those completing the study and/or having a week 8 BP reading. Seated BP, except for the telmisartan study which reported supine readings.

*Response defined as DBP <90 mmHg or a decrease from baseline of ≥10 mmHg.

*Marketed combination is 150/12.5 mg.

*Maximum in Europe.

*Maximum in United States.

**Abbreviations:** BP, blood pressure; DBP, diastolic BP; HCTZ, hydrochlorothiazide; SBP, systolic BP.
respiratory tract infections were also more frequent with olmesartan medoxomil/HCTZ than with placebo (7% vs 0%) (Daiichi Sankyo, Inc. 2005).

**Discussion**

Although it is generally recommended that antihypertensive therapy be initiated with a single agent, it is recognized that most patients will eventually require combination therapy to achieve recommended BP goals (Chobanian et al 2003; European Society of Hypertension 2003; Whitworth 2003). Indeed, JNC 7 suggests that in patients with Stage 2 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg), treatment should be initiated with two antihypertensive agents (Chobanian et al 2003; European Society of Hypertension 2003). Combination therapy typically consists of drugs from different classes with complementary mechanisms of action, such as a thiazide diuretic plus an agent that acts on the RAS (European Society of Hypertension 2003; Chobanian et al 2003).

Olmesartan medoxomil/HCTZ is one such combination, and is available as fixed-dose, once-daily preparations indicated for the treatment of hypertension, although not indicated for first-line therapy. In clinical trials, olmesartan medoxomil/HCTZ has demonstrated greater antihypertensive efficacy than either component as monotherapy (Chrysant et al 2004; Sellin et al 2005) and appears to compare favorably with other ARB/HCTZ combinations (Conlin et al 2000; McGill and Reilly 2001; Sachse et al 2002; Ram 2004; Lacourciere et al 2005; Neutel et al 2005; Rump et al 2006) and other fixed-dose combinations from different antihypertensive drug classes (Ball et al 2001; Quan et al 2006). However, limited head-to-head trials suggest the need for additional comparative trials in order to determine adequately potential differences in the BP-lowering effects and BP goal attainment rates achievable with these combination products.

It is well known that hypertension outcomes can be improved in clinical practice by setting target BP goals and providing physicians with easy-to-follow treatment algorithms (Singer et al 2002; Neutel et al 2004). A target level of <140/90 mmHg is recommended for patients with uncomplicated hypertension and no evidence of diabetes or renal disease (Chobanian et al 2003; European Society of Hypertension 2003; Whitworth 2003). Importantly, in an open-label trial, 9 out of 10 patients with Stage 1 hypertension, and more than half of patients with Stage 2 hypertension achieved an aggressive BP goal of ≤130/85 mmHg when treated with olmesartan medoxomil/HCTZ (Neutel et al 2006).

It is known that systolic hypertension is a better predictor of future cardiovascular morbidity than diastolic hypertension, especially in older patients (Izzo et al 2000; European Society of Hypertension 2003). However, SBP is often more difficult to control than DBP (Swales 1999; Mancia et al 2002). Treatment algorithms based on olmesartan medoxomil/HCTZ have been shown to significantly reduce SBP, in addition to DBP, in patients with Stage 1 and Stage 2 hypertension, allowing the majority of patients in both groups to achieve the SBP goal of ≤140 mmHg (Neutel et al 2006).

Various factors affect compliance and persistency with antihypertensive treatment. Long-term compliance has been shown to be better if initial therapy is well tolerated and the efficacy response is reasonably good (Caro et al 1999).

**Table 2** Antihypertensive efficacy of other angiotensin II receptor blocker/HCTZ combinations based on indirect comparison through a meta-analysis of randomized, double-blind, controlled trials assessing cuff BP in hypertensive patients with a DBP of 95–115 mmHg. Results are shown for starting dosages in the United States or Europe for each combination (Conlin et al 2000). For indirect comparative purposes, data for the starting dosage of olmesartan medoxomil/HCTZ from a randomized, double-blind, controlled trial in patients with Stage 1 or Stage 2 hypertension are also tabulated (Chrysant et al 2004; Rump et al 2006)

| Treatment            | Dosage (mg/day) | Mean absolute reduction from baseline (mmHg) | Absolute response rate<sup>b</sup> (%) |
|----------------------|-----------------|---------------------------------------------|---------------------------------------|
|                      |                 | SBP  | DBP  |                                             |
| Candesartan/HCTZ     | 8/12.5          | 20.6 | 9.9  | 56                                           |
| Irbesartan/HCTZ      | 150/12.5        | 16.1 | 12.4 | 66                                           |
| Losartan/HCTZ        | 50/12.5         | 16.5 | 12.0 | 70                                           |
| Valsartan/HCTZ       | 80/12.5         | 19.7 | 13.6 | 66                                           |
| Olmesartan medoxomil/HCTZ<sup>c</sup> | 20/12.5        | 20.1 | 16.4 | 79                                           |

<sup>a</sup>Weighted average change in cuff SBP and DBP for the meta-analysis.

<sup>b</sup>Response defined as DBP <90 mmHg or a decrease from baseline of ≥10 mmHg.

<sup>c</sup>Results from a trial with olmesartan medoxomil/HCTZ that was not part of the meta-analysis.

**Abbreviations:** DBP, diastolic BP; HCTZ, hydrochlorothiazide; SBP, systolic BP.
Currently available once-daily, fixed-dose combinations, such as olmesartan medoxomil/HCTZ and other ARB/HCTZ combinations, may simplify treatment regimens. Olmesartan medoxomil/HCTZ is effective and allows lower doses of component agents to be used compared with monotherapy, minimizing the likelihood of adverse events associated with higher doses of HCTZ (Neutel 2001; Chrysant et al 2004). These features may enhance patients’ acceptance of therapy and potentially increase the likelihood that they will continue with therapy through each successive stage of the treatment algorithm.

In summary, olmesartan medoxomil/HCTZ is an effective and well-tolerated combination antihypertensive therapy. It provides greater antihypertensive efficacy than either component given as monotherapy, and may provide a useful treatment option in patients unable to achieve BP goal with monotherapy.

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