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Olmesartan Medoxomil/Amlodipine

Mark Sanford and *Susan J. Keam*
Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Philadelphia, Pennsylvania, USA

Contents

Abstract

▲ Olmesartan medoxomil/amlodipine is a fixed-dose combination of olmesartan medoxomil and amlodipine, both established antihypertensive agents. Dose titration with the individual constituent drugs is recommended before switching to the equivalent fixed-dose combination.

▲ In a randomized, double-blind, factorial trial in patients with mild to severe hypertension, 8 weeks of olmesartan medoxomil/amlodipine was more effective in reducing diastolic BP (DBP) and systolic BP (SBP) than placebo or equivalent dosages of olmesartan medoxomil or amlodipine as monotherapy.

▲ In two randomized, double-blind trials in patients with moderate to severe hypertension not adequately treated with amlodipine or olmesartan medoxomil monotherapy, 8 weeks of olmesartan medoxomil/amlodipine 20 mg/5 mg, 40 mg/5 mg or 40 mg/10 mg per day was more effective in reducing DBP and SBP than continuing treatment with olmesartan medoxomil 20 mg/day or amlodipine 5 mg/day monotherapy.

▲ More patients receiving olmesartan medoxomil/amlodipine at approved dosages than monotherapy recipients at equivalent dosages reached BP goals (42.5–51.0% vs 21.1–36.3% in the factorial trial and 44.5–54% vs 28.5–30% in the monotherapy comparisons).

▲ In the comparison with amlodipine monotherapy, >70% of olmesartan medoxomil/amlodipine recipients, some requiring upwards dosage adjustment, met BP goals.

▲ Olmesartan medoxomil/amlodipine was generally well tolerated in clinical trials. Peripheral oedema was significantly less common in olmesartan medoxomil/amlodipine 40 mg/10 mg per day than amlodipine monotherapy 10 mg/day recipients.

Features and properties of olmesartan medoxomil/amlodipine (Sevikar®)	
Indications	
Essential hypertension not adequately controlled by olmesartan medoxomil or amlodipine monotherapy	
Mechanism of action	
Combined effects of an angiotensin II receptor antagonist (olmesartan) and a dihydropyridine calcium channel antagonist (amlodipine)	
Dosage and administration	
Recommended initial daily dosage	One tablet of olmesartan medoxomil/amlodipine 20 mg/5 mg, 40 mg/5 mg or 40 mg/10 mg (initiated at the current monotherapy dosage)
Daily dosage in the event of an inadequate response	Uptitration is recommended (from 20 mg/5 mg to 40 mg/5 mg, or from 40 mg/5 mg to 40 mg/10 mg)
Pharmacokinetic profile of the constituent drugs in healthy adults after single doses of olmesartan medoxomil/amlodipine 20 mg/5 mg, 40 mg/5 mg or 40 mg/10 mg	
Time to peak plasma concentration	Olmesartan 1.5–2 h; amlodipine 6–8 h
Terminal plasma elimination half-life	Olmesartan 10–15 h; amlodipine 35–50 h
Most frequent treatment-related adverse events	
Headache, dizziness, peripheral oedema	

Hypertension is a common disorder, with an overall age- and sex-adjusted prevalence in European countries of 44.2% in persons 35–64 years of age.[1] It is an established risk factor for cardiovascular diseases, including ischaemic heart disease and stroke, and these disorders account for one-third of all deaths globally.[2] The WHO reports that hypertension is responsible for ≈7 million premature deaths annually, contributing 4.5% to the total global burden of disease.[2]

Current European guidelines note that there is strong evidence that antihypertensive drugs lower the risk of morbidity and mortality resulting from non-fatal and fatal stroke (by ≈30–40%), coronary events (by 20%) and heart failure (percent reduction not reported).[3] Greater reductions in BP are associated with greater reductions in disease events, especially in patients with diabetes mellitus.[3] In patients with diabetes or with high cardiovascular risk, the European guidelines recommend a target BP level of ≤130/80 mmHg; for other patients, the BP target level is ≤140/90 mmHg.[3]

When antihypertensives are required, treatment should be initiated with a thiazide diuretic, calcium channel antagonist (calcium channel blocker [CCB]), ACE inhibitor, angiotensin II receptor antagonist (angiotensin II receptor blocker [ARB]) or a β-adrenergic receptor antagonist (β-blocker).[3] However, for a majority of patients, effective treatment will require a combination of two or more of these drugs.[3] European guidelines recommend combined drug treatment as the preferred first step in patients with high total cardiovascular risk or with hypertension grade 2 or 3 in severity (systolic BP [SBP] ≥160 mmHg and/or diastolic BP [DBP] ≥100 mmHg). Once a full response is established with the coadministration of two separate drugs, consideration can be given to using a fixed-dose combination, preferably once daily.[3]

Olmesartan medoxomil/amlodipine (Sevikar®), a fixed-dose formulation of the angiotensin II type 1 (AT_1) receptor blocker olmesartan medoxomil and the dihydropyridine CCB amlodipine, is approved in several European countries for once-daily administration in patients with essential hypertension who have not responded adequately to monotherapy with olmesartan medoxomil or amlodipine, or who are receiving separate tablets as combination therapy.[4,5] In the US, the fixed-dose formulation is marketed as Azor™ and is approved for the treatment of hypertension, alone or with other antihypertensive agents.[6] This article focuses, from an EU perspective, on efficacy and tolerability studies of olmesartan medoxomil/amlodipine in patients with hypertension, with a brief overview of its pharmacological properties. Medical literature on the use of olmesartan medoxomil/amlodipine in hypertension was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

The combined use of an ARB with a CCB is likely to have a greater antihypertensive effect than the drugs used alone, because different BP control mechanisms are affected, agonistic angiotensin II effects are preserved, and because targeting different mechanisms may reduce or prevent compensatory activity of the renin-angiotensin-aldosterone system (RAAS).[7] As pharmacodynamic studies of the effects of the olmesartan medoxomil/amlodipine combination on the RAAS are not available, this profile is restricted to a brief overview of the established mechanisms of action of olmesartan medoxomil[8] and amlodipine,[9,10] and findings from a recent study into the effects of olmesartan medoxomil plus amlodipine on insulin sensitivity and inflammation markers (available as an abstract).[11]

- Olmesartan medoxomil is an orally administered prodrug of olmesartan, a non-peptide ARB that has high selectivity for the AT_1 receptor, to which it is highly bound.[8] Olmesartan does not bind to the type 2 receptor.[8] Activation of the AT_1 receptor by angiotensin II (the primary vasoactive peptide of the RAAS) produces arteriolar vasoconstriction, increased sympathetic nervous system activity, increased salt and water retention and aldosterone secretion.[8] Aldosterone also causes salt and water

retention and an increase in blood volume. Olmesartan is presumed to reduce BP by blocking the vasoconstrictor and aldosterone-secreting effects of angiotensin II.[8]

- Consistent with this mechanism of action, animal and human studies show that the effects of olmesartan medoxomil on BP parallel the effects on the RAAS.[8] In animal models and clinical studies in patients with diabetes, chronic renal disease or hypertension with or without metabolic syndrome, olmesartan medoxomil had protective effects on end organs that are affected by the pathological changes occurring in hypertension.[8] It appears that these effects are to some extent independent of the BP-lowering effect.[8]

- In patients with hypertension, olmesartan medoxomil produces a gradual and sustained dose-dependent reduction in arterial BP, without first-dose hypotension, tachyphylaxis during extended treatment or rebound hypertension when treatment is discontinued abruptly.[5] Nevertheless, special care is required when initiating treatment with olmesartan medoxomil in patients who are at increased risk for postural hypotension, including the elderly and patients with hypovolaemia or sodium depletion.[5]

- A once-daily dosage of olmesartan medoxomil has the same antihypertensive effect as the same total daily dosage administered in two divided doses.[5]

- Amlodipine is a dihydropyridine CCB that reduces the influx of extracellular calcium into cardiac and vascular smooth muscle cells via L-type calcium channels.[9] Amlodipine has a greater effect on calcium influx in vascular smooth muscle cells in arteries and arterioles than in cardiac muscle cells, and has no effect on serum calcium levels.[6] As a result of the relaxation of arterial smooth muscle, vessel dilation is observed in arteries and arterioles.[9] This reduces peripheral vascular resistance and lowers BP.[9] Long-term oral administration of amlodipine has little or no effect on heart rate, cardiac conduction, plasma lipid levels, insulin sensitivity, blood glucose, blood insulin or plasma catecholamine levels, and plasma renin activity or aldosterone levels.[5,6,9]

- In contrast with short-acting dihydropyridine CCBs, amlodipine has a gradual and sustained antihypertensive effect over 24 hours in patients with mild to moderate hypertension.[9] Amlodipine does not cause first-dose hypotension, postural hypotension, tachyphylaxis with long-term treatment or rebound hypertension when treatment is discontinued abruptly, and a normal circadian BP pattern is preserved.[9]

- As with other CCBs, amlodipine produces a small increase in cardiac index, during exercise and at rest, in patients with normal left ventricular function.[6] In patients with heart failure, amlodipine was not associated with any indications of clinical deterioration, increased morbidity or risk of death.[5] Amlodipine increases renal blood flow, lowers renovascular resistance and increases the glomerular filtration rate, without affecting proteinuria or the filtration fraction.[5,9]

- In non-diabetic patients with hypertension and metabolic syndrome ($n = 120$), treatment with olmesartan medoxomil 20–40 mg/day plus amlodipine 5–10 mg/day for 24 weeks was associated with significant reductions from baseline in fasting blood insulin levels and insulin resistance index (by 14% and 16%; both $p < 0.01$ vs baseline) and a 14% increase in plasma adiponectin level ($p < 0.01$ vs baseline), whereas 24 weeks of treatment with olmesartan medoxomil 20–40 mg/day plus hydrochlorothiazide 12.5–25 mg/day had no significant effect on these parameters.[11]

- Olmesartan medoxomil plus amlodipine was also associated with significant ($p < 0.05$) reductions from baseline in all seven inflammation markers measured, while olmesartan medoxomil plus hydrochlorothiazide was associated with a significant ($p < 0.05$) reduction in one marker only.[11]

2. Pharmacokinetic Profile

This section provides an overview of the pharmacokinetic properties of olmesartan medoxomil and amlodipine.[5,8,9] It also reviews fully published pharmacokinetic data for fixed-dose olmesartan

medoxomil/amlodipine administered orally at recommended dosages in healthy volunteers[12] and from a population pharmacokinetic study that included healthy volunteers and a subset of hypertensive patients enrolled in the COACH (Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure) trial (see section 3 for trial details).[13]

- Olmesartan medoxomil is a prodrug that is completely metabolized by esterases in the gastrointestinal (GI) tract to its active metabolite olmesartan, which is not metabolized further.[5,8] It is rapidly absorbed from the GI tract with a time to maximum concentration (t_{max}) of ≈2 hours.[5] Orally administered olmesartan medoxomil has an absolute bioavailability of 25.6% and is 99.7% bound to plasma protein.[5] After intravenous administration, the mean volume of distribution is low at 16–29 L.[5]
- Olmesartan steady-state concentrations are reached after the first few doses and there is no further accumulation after repeated administration over 14 days.[5] At steady state, olmesartan is cleared quickly from the body, with a plasma terminal elimination half-life of 10–15 hours. Olmesartan is cleared mainly through hepatobiliary excretion, with 10–16% excreted in the urine. As olmesartan is chiefly excreted in bile, olmesartan medoxomil/amlodipine is contraindicated in patients with biliary obstruction.[5]
- Amlodipine is slowly absorbed from the GI tract, with a t_{max} of 6–12 hours after oral administration of therapeutic doses.[5] Unchanged amlodipine is estimated to have a bioavailability of 64–80% and is ≈98% bound to plasma protein, with a volume of distribution of ≈20 L/kg. After repeated daily oral administration, the time to amlodipine steady state is 7–8 days.[5] Amlodipine undergoes extensive metabolism in the liver to form inactive metabolites[9] and is cleared slowly from the body, with a plasma elimination half-life of 35–50 hours.[5] It is excreted mainly in the urine.[5]

Combination Therapy

- Orally administered, fixed-dose olmesartan medoxomil/amlodipine met prespecified drug systemic exposure bioequivalence criteria when compared with equivalent doses of olmesartan medoxomil and amlodipine coadministered as separate preparations in single- or multiple-dose studies.[12] For example, with the 40 mg/10 mg combination, peak plasma concentrations of olmesartan and amlodipine were 833.3 and 7.6 ng/mL, and area under the plasma concentration-time curve for the dose administration interval values were 5374.2 and 424.8 ng • h/mL after a single dose.[12] Corresponding values for olmesartan medoxomil 40 mg and amlodipine 10 mg as separate components were 810.3 and 7.4 ng/mL, and 5418.6 and 410.9 ng • h/mL.[12]
- The total olmesartan and amlodipine systemic exposures after administration of olmesartan medoxomil/amlodipine were dose proportional over a range of 10 mg/5 mg to 40 mg/10 mg.[12] After oral administration of olmesartan medoxomil/amlodipine, t_{max} was 1.5–2 hours for olmesartan and 6–8 hours for amlodipine.[5]
- Olmesartan medoxomil/amlodipine can be taken with or without food,[5] as there was no difference in olmesartan and amlodipine bioavailability when olmesartan medoxomil/amlodipine 40 mg/10 mg was administered to healthy adults (n = 27) while fasting compared with after a high-fat breakfast.[12]
- There were no pharmacokinetic interactions between olmesartan and amlodipine when olmesartan medoxomil and amlodipine were coadministered as a fixed-dose combination or as separate tablets[12] and the oral clearance of either drug was not affected.[13]
- Although dosage adjustment with olmesartan medoxomil/amlodipine dosage regimen is not required for elderly patients, caution is needed when increasing the dosage in the elderly patient (section 5), as studies with the constituent drugs show that systemic exposure to olmesartan and amlodipine is increased in patients ≥65 years of age in comparison with individuals from a younger age group.[5]
- Olmesartan medoxomil/amlodipine should not be used in patients with severe renal impairment, and dosage adjustments are necessary for patients with mild to moderate renal impairment, as systemic

exposure to olmesartan is increased in these patients (section 5).[5] In patients with mild to moderate hepatic impairment, systemic exposure to olmesartan and amlodipine is increased relative to healthy volunteers.[5] Olmesartan medoxomil/amlodipine is contraindicated in patients with severe hepatic impairment (section 5).[5]

- No clinically important pharmacokinetic drug interactions were detected when olmesartan medoxomil or amlodipine were coadministered with other drugs commonly used in the treatment of hypertension.[5,8]
- Olmesartan medoxomil is not metabolized by cytochrome P450 (CYP) enzymes, and drug-drug interactions with agents metabolized by this system are unlikely.[5] However, amlodipine is metabolized by CYP enzymes, and there is the potential for drug interactions when amlodipine is coadministered with CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) and inducers (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone, rifampicin [rifampin], *Hypericum perforatum* [St John's wort]). Therefore, caution is advised when coadministering any of these drugs with olmesartan medoxomil/amlodipine.[5]
- Olmesartan medoxomil/amlodipine should not be used concomitantly with lithium or potassium supplements or other agents affecting potassium levels, as there is the potential for clinically important pharmacokinetic drug interactions (reversible increases in serum lithium concentration and toxicity or increased serum potassium) when ARBs are coadministered with these agents.[5] Caution should also be exercised in coadministering ARBs with NSAIDs, which may lead to attenuation of antihypertensive effects.[5]

3. Therapeutic Efficacy

Clinical trials in patients with hypertension and/or other cardiovascular disorders have established that amlodipine[9,10] and olmesartan medoxomil[8] lower BP, and that the combination of the two drugs has an additive antihypertensive effect.[5] The efficacy of fixed-dose olmesartan medoxomil/amlodipine in patients with mild to severe hypertension was evaluated in COACH, a randomized, double-blind, placebo-controlled, multicentre trial (n = 1940).[14] Two further randomized, double-blind, multinational trials evaluated the efficacy of olmesartan medoxomil/amlodipine in patients with moderate to severe hypertension who did not respond adequately to amlodipine (n = 755)[15] or olmesartan medoxomil (n = 538)[16] monotherapy. The trials are fully published, except for the trial in patients not responding adequately to olmesartan medoxomil monotherapy, which is available as an abstract with poster.[16] Several prespecified subgroup analyses[17-23] and an open-label extension[24] from the COACH trial are available as abstracts with posters.

COACH Trial

The COACH trial included patients aged ≥18 years with mild to severe hypertension, defined as a seated DBP of 95–120 mmHg at two separate visits; a ≤10 mmHg difference between the two measurements was also required.[14] Patients who smoked more than one pack of cigarettes per day, or had a history of cardiovascular disease or uncontrolled diabetes were excluded. The trial followed a factorial design with all patients meeting inclusion criteria randomized to 8 weeks of olmesartan medoxomil monotherapy (10, 20 or 40 mg/day), amlodipine monotherapy (5 or 10 mg/day), all possible combinations of olmesartan medoxomil and amlodipine, or placebo (12 treatment groups in total). Patients who were treatment-naive were immediately randomized to receive study therapy, while those already receiving antihypertensive therapy at screening underwent a 2-week washout period prior to assessment for eligibility and randomization.[14] Regimens involving dosages or combinations that are not approved in the EU are not discussed in this section.

The primary endpoint was the change in mean seated DBP from baseline to the end of double-blind treatment.[14] Statistical analyses for the primary endpoint were on the intent-to-treat (ITT) population with last-observation-carried-forward (LOCF) imputation; the ITT population included patients

who had a BP measurement at baseline and at least one BP measurement after taking at least one dose of study medication. Secondary efficacy endpoints included the change from baseline to 8 weeks in mean seated SBP and the proportions of patients with and without diabetes achieving a prespecified BP goal (<130/80 mmHg in patients with diabetes and <140/90 mmHg for patients without diabetes). BP was the mean of three seated recordings measured with an automated BP monitor at 2, 4, 6 and 8 weeks.[14]

In total, 1923 patients were included in the primary efficacy analysis (1689 patients completed 8 weeks of treatment).[14] In randomized patients, the mean age was 54 years, 54% were male, 71% were white, 25% were black, the mean BP at baseline was 164/102 mmHg (79% had stage 2 hypertension with SBP ≥160 mmHg or DBP ≥100 mmHg), 14% had diabetes, 65% had a body mass index (BMI) ≥30 kg/m^2 and 66% were already receiving antihypertensive medication.[14]

- Fixed-dose olmesartan medoxomil/amlodipine was associated with dose-dependent reductions in seated DBP (primary endpoint) from baseline to 8 weeks that were greater than those with equivalent dosages of olmesartan medoxomil or amlodipine when given as monotherapy.[14] Reductions from baseline in mean seated DBP with olmesartan medoxomil/amlodipine 20 mg/5 mg, 40 mg/5 mg or 40 mg/10 mg per day (−14.0 to −19.0 mmHg) were significantly greater ($p < 0.001$) than those with the corresponding dosages of olmesartan medoxomil (−9.2 and −10.2 mmHg) or amlodipine (−9.4 and −12.7 mmHg) monotherapy. Changes in mean seated DBP from baseline at 8 weeks were significant ($p < 0.001$) for all combination therapy and monotherapy dosages and placebo (−3.1 mmHg).[14]
- Dose-dependent reductions in seated SBP were also larger with olmesartan medoxomil/amlodipine than with an equivalent dosage of olmesartan medoxomil or amlodipine given as monotherapy.[14] The mean change from baseline in seated SBP was significantly greater ($p < 0.001$) in patients receiving olmesartan medoxomil/amlodipine (−23.6 to −30.1 mmHg with dosages of 20 mg/5 mg to 40 mg/10 mg per day) than with corresponding olmesartan medoxomil (−11.5 to −16.1 mmHg) or amlodipine (−14.9 to −19.7 mmHg) monotherapy. A significant change in seated SBP from baseline to 8 weeks was observed with all combination and monotherapy dosages (all $p < 0.001$) and with placebo (−4.8 mmHg; $p < 0.05$).[14]
- A significantly greater proportion of olmesartan medoxomil/amlodipine recipients met prespecified BP goals than monotherapy recipients.[14] The proportions of patients achieving the prespecified BP goal (<130/80 mmHg and <140/90 mmHg in patients with and without diabetes) after 8 weeks of treatment were 42.5–51.0% with olmesartan medoxomil/amlodipine 20 mg/5 mg, 40 mg/5 mg or 40 mg/10 mg per day, compared with 26.4% or 36.3% with olmesartan medoxomil 20 or 40 mg/day monotherapy and 21.1% and 32.5% with amlodipine 5 or 10 mg/day monotherapy ($p < 0.005$ for olmesartan medoxomil/amlodipine vs the component monotherapies). Only 8.8% of placebo recipients achieved BP goals.[14]
- The largest reductions in seated BP with the fixed-dose olmesartan medoxomil/amlodipine combination were evident by week 2, plateaued by week 4, and subsequent reductions were minimal.[14]
- The prespecified subgroup analyses showed that olmesartan medoxomil/amlodipine led to significant reductions from baseline in seated DBP and seated SBP, regardless of age (above or below 65 years),[17] sex,[18] ethnicity (Black vs non-Black, Hispanic/Latino vs non-Hispanic/non-Latino),[20] the presence or absence of diabetes,[19] BMI (<30 or ≥30 kg/m^2),[21] hypertension stage[22] and previous treatment with antihypertensive agents.[23]
- During the 44-week, open-label extension study, 54% (903 of 1672) of patients continued to receive olmesartan medoxomil/amlodipine combination therapy.[25] Of these, 378 patients required uptitration from the 40 mg/5 mg to the 40 mg/10 mg per day dosage. BP goals were achieved by 80% of the patients who continued at olmesartan medoxomil/amlodipine 40 mg/5 mg per day and 71% of the patients uptitrated to olmesartan medoxomil/amlodipine 40 mg/10 mg per day. The remaining patients required the addition of hydrochlorothiazide

12.5 mg/day (n = 287) or 25 mg/day (n = 419) to olmesartan medoxomil/amlodipine 40 mg/10 mg per day, because BP goals had not been reached on combination therapy. With the addition of hydrochlorothiazide, 67% and 46% of patients achieved the target BP goal.[25]

In Patients Not Adequately Responsive to Amlodipine Monotherapy

The comparison with amlodipine monotherapy included patients aged ≥18 years with moderate to severe hypertension.[15] Patients already receiving amlodipine monotherapy were required to have a seated SBP ≥140 mmHg, seated DBP ≥90 mmHg and mean DBP ≥80 mmHg by 24-hour ambulatory BP monitoring (ABPM), with ≥30% daytime DBP readings >85 mmHg. Treatment-naive patients and those who had completed a 1- to 2-week washout period after ceasing other antihypertensives were required to have a seated SBP ≥160 mmHg, seated DBP ≥100 mHg and mean DBP ≥84 mmHg by 24-hour ABPM, with ≥30% of daytime DBP readings >90 mmHg. Patients were excluded if they had secondary or malignant hypertension, mean seated DBP >115 mmHg or mean seated SBP >200 mmHg, a history of cardiovascular disease or clinically significant systemic disease, or had not responded to previous treatment with two or more conventional antihypertensive agents.[15]

All patients entered an 8-week, open-label, monotherapy run-in period with amlodipine 5 mg.[15] At the conclusion of the monotherapy phase, patients who had not reached BP goals with monotherapy qualified for the 8-week double-blind trial. Eligible patients were randomized to amlodipine 5 mg/day plus placebo or to olmesartan medoxomil/amlodipine 10 mg/5 mg, 20 mg/5 mg or 40 mg/5 mg per day for 8 weeks. Patients then entered a final 8-week double-blind treatment phase that included uptitration of olmesartan medoxomil/amlodipine dosages in patients who did not respond to treatment (seated SBP ≥140 mmHg and seated DBP ≥90 mmHg) during the first 8-week double-blind phase; responders continued the randomized treatment.[15] Only regimens involving dosages or combinations approved in the EU are discussed further.

The primary endpoint was the mean change in trough seated DBP (measured just prior to taking the daily dose of medication) from the end of the open-label monotherapy run-in period (baseline) to the end of double-blind treatment.[15] The primary statistical analyses were conducted on the ITT population (defined as in COACH) using LOCF imputation. Important secondary endpoints included the mean changes in trough seated DPB (baseline to 4 weeks) and seated SBP (baseline to 4 and 8 weeks), and the proportion of patients reaching the prespecified BP goal (<130/80 mmHg in patients with diabetes and <140/90 mmHg in those without diabetes) at the end of each double-blind treatment phase.[15]

A total of 755 patients were randomized and 746 patients were included in the primary efficacy analysis (706 and 692 patients completed the initial and subsequent double-blind treatment phases).[15] The mean patient age was 55.8 years, 61.1% were male, 7.2% had diabetes, the mean BMI was 28.9 kg/m^2 and 78.7% were already receiving antihypertensive medication (42.5% were taking amlodipine).[15]

- Fixed-dose olmesartan medoxomil/amlodipine was efficacious in reducing BP in patients with moderate to severe hypertension who had not responded to 8 weeks of amlodipine[15] monotherapy. Compared with continuing amlodipine monotherapy, all dosages of olmesartan medoxomil/amlodipine led to significantly greater changes in mean seated DBP from baseline to the end of the 8-week, double-blind treatment (primary endpoint) [figure 1]. The incremental reductions in seated DBP in the olmesartan medoxomil/amlodipine recipients who received approved dosages were 3.8 and 3.9 mmHg for olmesartan medoxomil/amlodipine 20 mg/5 mg and 40 mg/5 mg per day recipients over amlodipine 5 mg/day recipients.[15]
- Patients treated with fixed-dose olmesartan medoxomil/amlodipine also experienced greater reductions in mean seated SBP from baseline to 8 weeks than amlodipine and olmesartan medoxomil monotherapy recipients (figure 1).

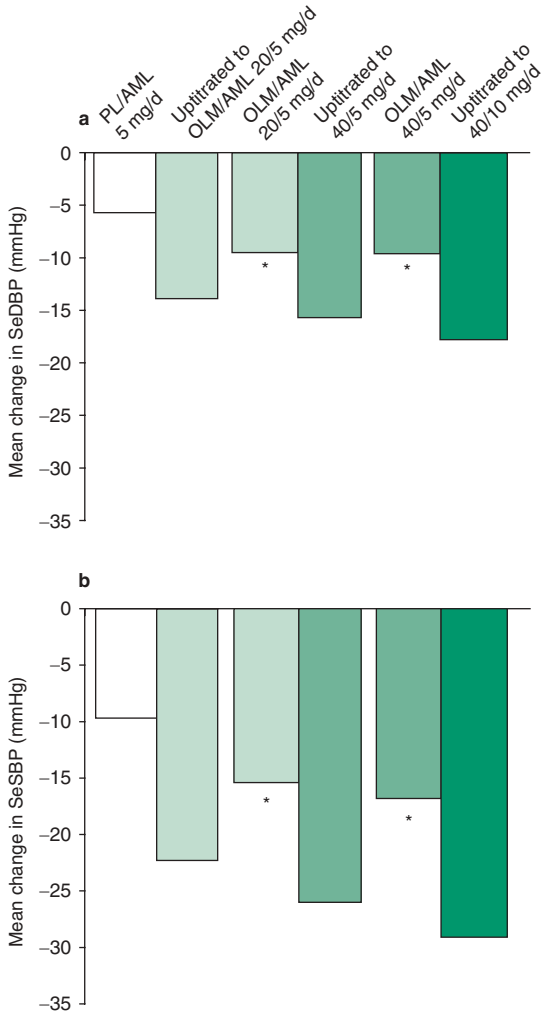

Fig. 1. Efficacy of fixed-dose olmesartan medoxomil/amlodipine (OLM/AML) in patients with moderate to severe hypertension who had not achieved BP goals after 8 weeks of AML monotherapy.[15] Mean change in (**a**) seated diastolic BP (SeDBP) [primary endpoint] and (**b**) seated systolic BP (SeSBP) [secondary endpoint] from baseline to the end of 8 weeks (initial double-blind treatment period) and 16 weeks (uptitration phase) of treatment in a randomized, double-blind trial. Patients were treated with placebo (PL)/AML 5 mg/day (n = 184) or OLM/AML 20 mg/5 mg (n = 187) or 40 mg/5 mg per day (n = 186) during the initial double-blind treatment phase. Data for a combination not approved in the EU (OLM/AM 10 mg/5 mg per day) [n = 189] are not shown. Patients who did not respond to treatment (SeSBP ≥140 mmHg and SeDBP ≥90 mmHg) during the first 8-week double-blind phase were uptitrated to OLM/AML 20 mg/5 mg (number of patients not reported), 40 mg/5 mg (n = 118) or 40 mg/10 mg (number of patients not reported) per day. Mean baseline BP values across all treatment groups were 164/102 to 166/102 mmHg. * $p < 0.0001$ vs PL/AM; statistical analyses not reported for changes from baseline during the uptitration phase.

The incremental reductions in seated SBP in patients who received approved dosages were 5.7 and 7.1 mmHg for olmesartan medoxomil/amlodipine 20 mg/5 mg and 40 mg/5 mg per day recipients over amlodipine 5 mg/day recipients.[15]

- During the uptitration phase of the amlodipine comparison, patients experienced additional BP reductions (figure 1). Total changes from baseline in mean seated DBP ranged from −13.9 mmHg, in patients receiving placebo/amlodipine 5 mg/day uptitrated to olmesartan medoxomil/amlodipine 20 mg/5 mg per day, to −17.8 mmHg in patients uptitrated from olmesartan 40 mg/5 mg to 40 mg/10 mg per day; the change from baseline in mean seated SBP ranged from −22.3 mmHg to −29.1 mmHg.[15]
- More patients treated with the combined formulation achieved BP goals during the initial double-blind treatment phase than amlodipine monotherapy recipients.[15] At 8 weeks, 54% and 51% of olmesartan medoxomil/amlodipine 20 mg/5 mg and 40 mg/5 mg per day and 30% of placebo/amlodipine 5 mg/day recipients met BP goals (both $p < 0.0001$ vs monotherapy).
- For patients requiring a dosage increase during the uptitration phase, an additional 28–47% of olmesartan medoxomil/amlodipine recipients met BP goals.[15] By the end of the study (initial and uptitration phases), >70% of patients who received olmesartan medoxomil/amlodipine, with or without uptitration, met BP goals.[15]

In Patients Not Adequately Responsive to Olmesartan Medoxomil Monotherapy

The comparison with olmesartan medoxomil used the same age and BP inclusion criteria, similar exclusion criteria, and the same procedures as the comparison with amlodipine.[16] After inclusion, all patients entered an 8-week, open-label, monotherapy run-in period with olmesartan medoxomil 20 mg/day. At the conclusion of the monotherapy phase (baseline), patients who had not reached BP goals (seated SBP ≥140 mmHg, seated DBP ≥90 mmHg and mean DBP ≥80 mmHg by 24-hour ABPM, with ≥30% daytime DBP readings

>85 mmHg, as in the comparison with amlodipine) qualified for the 8-week double-blind trial. These patients were randomized to olmesartan medoxomil 20 mg/day plus placebo or olmesartan medoxomil/amlodipine 20 mg/5 mg or 20 mg/10 mg per day. The trial used the same primary and secondary endpoints and analytic approach as the comparison with amlodipine, but there was no uptitration phase.[16] Only regimens involving dosages or combinations approved in the EU are discussed further.

A total of 538 patients were randomized and included in the efficacy analyses (522 patients completed the study).[16] Across treatment arms, the mean patient age was 56–58 years, 46–52% were male, 5–10% had diabetes, the mean BMI was approximately 29 kg/m^2 and 59–73% were taking antihypertensive drugs. Mean baseline BP values ranged from 155/97 to 156/98 mmHg.[16]

- Fixed-dose olmesartan medoxomil/amlodipine was efficacious in reducing BP in patients with moderate to severe hypertension who had not responded to 8 weeks of olmesartan medoxomil monotherapy.[16] Compared with continuing olmesartan medoxomil monotherapy, both dosages of olmesartan medoxomil/amlodipine led to significantly greater changes in mean seated DBP from baseline to the end of the 8-week double-blind treatment period (primary endpoint). The incremental reduction in seated DBP with olmesartan medoxomil/amlodipine 20 mg/5 mg per day over olmesartan medoxomil 20 mg/day was 2.7 mmHg ($p = 0.0006$).[16]
- Patients treated with olmesartan medoxomil/amlodipine also experienced greater reductions from baseline to 8 weeks in mean seated SBP than olmesartan medoxomil monotherapy recipients.[16] The incremental reduction in seated SBP in patients who received olmesartan medoxomil/amlodipine 20 mg/5 mg per day was 5.9 mmHg over olmesartan medoxomil 20 mg/day monotherapy recipients ($p = 0.0001$).[16]
- More patients treated with the combined formulation achieved BP goals than olmesartan medoxomil monotherapy recipients.[16] At 8 weeks, 44.5% and 28.5% of olmesartan medoxomil/amlodipine 20 mg/5 mg per day and placebo/olmesartan medoxomil 20 mg/day monotherapy recipients met BP goals ($p = 0.0011$ vs monotherapy).[16]

4. Tolerability

Tolerability data for orally administered, fixed-dose olmesartan medoxomil/amlodipine are available from the randomized, double-blind trials described in section 3.

- During the 8-week, double-blind treatment phase of the COACH trial, olmesartan medoxomil/amlodipine was generally well tolerated and the majority of reported adverse events were mild in severity.[14] Across all treatment groups, 27% of patients reported at least one adverse event; the most common treatment-emergent adverse events occurring at a frequency ≥3% (excluding peripheral oedema) were headache (6.7%), dizziness (3.9%) and fatigue (3.2%). In total, 3.8% of patients withdrew from the trial because of adverse events that were thought to be treatment related.[14]
- The only serious treatment-related adverse event (nonfatal cerebrovascular event) was reported in an olmesartan medoxomil 20 mg/day recipient with hypertension that was not fully controlled.[14] Across all treatment groups during the double-blind treatment phase, few patients (0.5%) experienced hypotension (two affected patients were withdrawn from the study because of moderate or severe hypotension) and there were no clinically significant mean changes in laboratory tests.[14]
- There were no adverse events associated with longer-term use of olmesartan medoxomil/amlodipine beyond those expected with the component drugs used as monotherapy.[24] Among all patients from the COACH trial treated for a further 44 weeks ($n = 1684$) in an open-label extension at olmesartan medoxomil/amlodipine dosages of 40 mg/5 mg or 40 mg/10 mg per day (with or without hydrochlorothiazide 12.5 or 25 mg/day as required), the adverse events profile was similar to that seen in the double-blind phase, and only 2.2% of patients experienced hypotension.[24]
- Drug-related adverse events were relatively uncommon during the double-blind treatment phase of

the trials comparing olmesartan medoxomil/amlodipine with the respective monotherapies[15,26] and during the uptitration phase of the comparison with amlodipine monotherapy.[15] Treatment-related events were reported in 5.3–7.7% of patients receiving approved dosages of olmesartan medoxomil/amlodipine compared with 7.4% of amlodipine and 8.9% of olmesartan medoxomil monotherapy recipients.[15,26]

- In the comparison with amlodopine, the treatment-related adverse events (excluding peripheral oedema) reported most frequently with olmesartan medoxomil/amlodipine 20 mg/5 mg or 40 mg/5 mg per day compared with placebo/amlodipine 5 mg/day during the initial 8-week randomized phase were headache (0–2.1% vs 0.5%), dizziness (1.1–2.1% vs 0%), hypotension (both 1.1% vs 0%) and vertigo (0–0.5% vs 1.1%).[15] In the comparison with olmesartan medoxomil, the most common treatment-related adverse events occurring during the randomized phase in olmesartan medoxomil/amlodipine 20 mg/5 mg per day and olmesartan medoxomil 20 mg/day recipients were headache (3.3% and 1.7%), hyperkalaemia (both 1.1%) and dizziness (0.5 and 1.1%).[26]
- Few patients receiving combination therapy or monotherapy in either trial discontinued during double-blind treatment because of an adverse event (0.5–2.7%).[15,26]
- One patient treated with olmesartan medoxomil/amlodipine 40 mg/5 mg per day died of cerebral haemorrhage during the uptitration phase of the amlodipine comparison, but this was not thought to be related to study medications.[15] Throughout the open-label and double-blind treatment phases of the comparative trials, no patient experienced a serious adverse event that was thought by the investigators to be drug related.[15,26]

Peripheral Oedema

Peripheral oedema, unrelated to congestive heart failure, is a well recognized adverse event associated with CCBs.[10] It results from CCB-induced arteriolar vasodilation leading to increased capillary pressure that is uncompensated in the absence of venous vasodilation.[10] The addition of drugs that cause venous vasodilation, such as the ARBs and ACE inhibitors, have the potential to compensate for increased capillary blood flow and pressure and to reduce peripheral oedema.[10] Thus, the COACH trial specifically assessed patients in order to obtain a reliable estimate of the reduction in oedema that could be achieved by adding olmesartan medoxomil to amlodipine.[14] The presence of oedema was rated on a 5-point severity scale at all scheduled clinic visits.[14] In the comparisons of olmesartan medoxomil/amlodipine with the respective monotherapies, oedema was not evaluated separately from other adverse events.[15,26]

- Peripheral oedema was a commonly observed adverse event at baseline and throughout the COACH trial.[14] At baseline, 13.6% of randomized patients in the COACH trial had peripheral oedema that was most commonly graded as mild (11.1%).
- Peripheral oedema rates occurring during the 8-week randomized treatment phase in patients receiving olmesartan medoxomil/amlodipine at approved dosages, amlodipine or olmesartan medoxomil monotherapy at equivalent dosages or placebo are shown in figure 2. Treatment-related peripheral oedema was observed in 19.8% of patients during the trial and affected 12.3% of placebo recipients. As anticipated, it was more frequent in the amlodipine 10 mg/day group than in the combined formulation at the equivalent amlodipine dosage (figure 2).[14]
- Most cases of peripheral oedema occurring during the trial were mild or moderate in severity; severe oedema occurred in 0.3% of patients overall, and in 1.2% and 0.6% of amlodipine 10 mg and olmesartan medoxomil/amlodipine 40 mg/10 mg per day recipients, respectively.[14]
- Oedema was also reported in the comparisons of olmesartan medoxomil/amlodipine with the respective monotherapies, but at a lower frequency than in the COACH trial.[15,26] The specific rates were 0.5% and 1.1% in olmesartan medoxomil/amlodipine 20 mg/5 mg and 40 mg/5 mg per day recipients, 2.1% in amlodipine 5 mg/day recipients,[15] and 1.1% and 0.6% in olmesartan medoxomil/

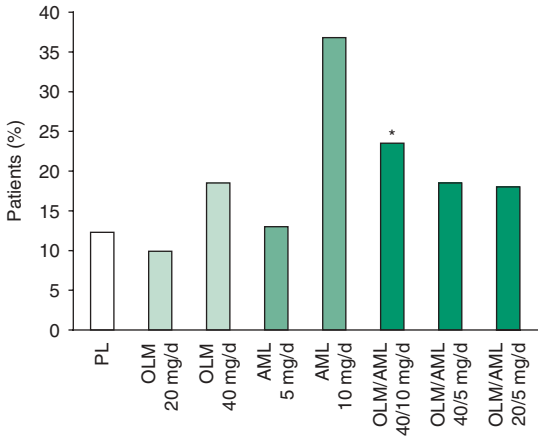

Fig. 2. Peripheral oedema in patients with mild to severe hypertension treated with olmesartan medoxomil/amlodipine (OLM/AML).[14] Percent of patients with peripheral oedema during the 8-week randomization phase of the COACH trial in patients treated with OLM/AML 20 mg/5 mg, 40 mg/5 mg and 40 mg/10 mg per day (approved dosages), OLM and AML monotherapy recipients who received equivalent dosages, and placebo (PL) recipients. * $p = 0.0011$ vs AML 10 mg/day.

amlodipine 20 mg/5 mg per day and olmesartan medoxomil 20 mg/day recipients.[16]

5. Dosage and Administration

In European countries where it is approved for the treatment of hypertension, olmesartan medoxomil/amlodipine 20 mg/5 mg once daily may be administered to patients whose BP is not adequately controlled by olmesartan medoxomil 20 mg/day or amlodipine 5 mg/day.[5] In patients whose BP is not controlled by olmesartan medoxomil/amlodipine 20 mg/5 mg per day, the dosage may be increased to 40 mg/5 mg once daily, and in patients whose BP is not controlled by olmesartan medoxomil/amlodipine 40 mg/5 mg per day, the dosage may be increased to 40 mg/10 mg once daily.[5]

Stepwise dosage titration of the individual component drugs is generally recommended before switching to the fixed-dose combination.[5] Patients may be switched from separate tablets of olmesartan medoxomil and amlodipine to olmesartan medoxomil/amlodipine at a dosage equivalent to that of the component drugs.[5]

Generally, no dosage adjustments are required in patients aged ≥65 years, but close BP monitoring is required when the maximum dosage of 40 mg olmesartan medoxomil is used.[5] There is no experience with olmesartan medoxomil dosages higher than 20 mg/day in patients with mild to moderate renal impairment (creatinine clearance [CL_{CR}] 20–60 mL/min).[5] Therefore, this olmesartan medoxomil dosage should not be exceeded in these patients. Olmesartan medoxomil/amlodipine is not recommended for patients with severe renal impairment (CL_{CR} <20 mL/min).[5]

Caution is required in patients with mild to moderate hepatic impairment, and the maximum daily dosage of olmesartan medoxomil in the combination in these patients is 20 mg.[5] Olmesartan medoxomil/amlodipine is contraindicated in patients with severe hepatic insufficiency or biliary obstruction.[5]

Olmesartan medoxomil/amlodipine is also contraindicated in patients with cardiogenic shock, unstable angina pectoris or myocardial infarction because of the effects of amlodipine.[5]

As with other drugs that act on the RAAS, olmesartan medoxomil (and therefore olmesartan medoxomil/amlodipine) is contraindicated for use in the second and third trimesters of pregnancy, and should be used with caution in the first trimester, because of risk to the developing fetus.[5]

Local prescribing information should be consulted for detailed information about contraindications, precautions, drug interactions and use in special patient populations.

6. Olmesartan Medoxomil/Amlodipine: Current Status

Fixed-dose olmesartan medoxomil/amlodipine is approved in several European countries for the treatment of essential hypertension in patients who are not adequately controlled by monotherapy with olmesartan medoxomil or amlodipine.[5] It is also approved for use in patients with essential hypertension already receiving these drugs as a free combination.[5] In the US, it is approved for the treatment of patients with essential hypertension, alone or with other hypertensive agents.[6] Dosage titration using

the component drugs is recommended before changing to the combined formulation.[5]

In double-blind trials, olmesartan medoxomil/amlodipine was more effective than olmesartan medoxomil or amlodipine monotherapy in reducing BP and achieving BP goals in patients with mild to severe hypertension and in patients with moderate to severe hypertension who had not responded adequately to olmesartan medoxomil or amlodipine monotherapy. Up to 50% of patients who had not responded to 8 weeks of monotherapy with the constituent drugs responded to treatment with fixed-dose olmesartan medoxomil/amlodipine and 28–47% of all patients who did not reach BP treatment goals at low dosages later responded during an 8-week uptitration phase; >70% of patients treated with olmesartan medoxomil/amlodipine reached BP goals by the end of the uptitration phase. Olmesartan medoxomil/amlodipine was generally well tolerated in all clinical trials. Peripheral oedema, an adverse event associated with CCBs, was significantly less common in fixed-dose olmesartan medoxomil/amlodipine than amlodipine monotherapy recipients in a trial that specifically evaluated this event.

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Correspondence: *Mark Sanford*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand.
E-mail: demail@adis.co.nz