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Amlodipine/Valsartan
Fixed-Dose Combination in Hypertension

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Contents

Abstract

▲ Amlodipine, a dihydropyridine calcium channel blocker, and valsartan, an angiotensin II receptor blocker, are established antihypertensive agents. Fixed-dose combinations of amlodipine/valsartan are available in several European countries and in the US. Individual dose titration with amlodipine and valsartan is generally recommended before changing to the fixed-dose combination.

▲ Amlodipine/valsartan, at approved dosage regimens, achieved significantly greater reductions in mean sitting diastolic and systolic blood pressure (BP) than amlodipine or valsartan monotherapy, or placebo in two randomized, double-blind, factorial trials in patients with mild to moderate hypertension.

▲ Approximately 80–90% of patients receiving approved dosages of amlodipine/valsartan achieved a response, defined as a mean sitting diastolic BP <90 mmHg or a ≥10 mmHg reduction from baseline.

▲ Subgroup analyses of data from the two trials showed that the antihypertensive efficacy of amlodipine/valsartan in the elderly, Black patients and those with stage 2 hypertension was consistent with that observed in the overall study population.

▲ Marked reductions in BP were also observed in patients whose BP was previously uncontrolled on monotherapy (with various antihypertensives) who were switched (without washout) to amlodipine/valsartan in a phase IIIb–IV study.

▲ Amlodipine/valsartan was generally well tolerated in clinical trials. In particular, the incidence of peripheral oedema was significantly lower in patients receiving amlodipine/valsartan than in those treated with amlodipine monotherapy.

Features and properties of amlodipine/valsartan (Exforge®)	
Indication	
Indication in the EU: for patients with hypertension whose blood pressure (BP) is not adequately controlled with amlodipine or valsartan monotherapy	
Indication in the US: for patients with hypertension whose BP is not adequately controlled with amlodipine (or another dihydropyridine calcium channel blocker [CCB]) alone or with valsartan (or another angiotensin II receptor blocker [ARB]) alone	
Mechanism of action	
Combined effects of a dihydropyridine CCB (amlodipine) and an ARB (valsartan)	
Dosage and administration	
Recommended dosage in the EU	One tablet of amlodipine/valsartan (5 mg/80 mg, 5 mg/160 mg or 10 mg/160 mg) once daily
Recommended dosage in the US	One tablet of amlodipine/valsartan (5 mg/160 mg, 10 mg/160 mg, 5 mg/320 mg or 10 mg/320 mg) once daily
Route of administration	Oral
Pharmacokinetic profile (of individual components unless otherwise stated)	
Time to peak plasma concentration (fixed-dose combination)	Amlodipine: 6–8 h; valsartan: 3 h
Absolute bioavailability	Amlodipine: 64–80%; valsartan 23%
Volume of distribution	Amlodipine: 21 L; valsartan: 17 L
Plasma protein binding	Amlodipine: 97.5%; valsartan: 94–97%
Elimination half-life	Amlodipine: 30–50 h; valsartan: 6 h
Most frequently reported adverse events	
Peripheral oedema, headache, nasopharyngitis, upper respiratory tract infection, dizziness	

Numerous drugs from various classes are available for the management of hypertension; however, most patients will require a combination of antihypertensive agents to achieve target blood pressure (BP) levels.[1,2] For high-risk patients with hypertension, such as those with diabetes mellitus or renal impairment, combination therapy is almost always required (≈90% of patients) to achieve BP goals (<130/80 mmHg).[2,3] Fixed-dose combinations of amlodipine/valsartan (Exforge®)[1] are available in several European countries and in the US for once-daily oral administration in patients with hypertension who have not had an adequate response to amlodipine or valsartan monotherapy (EU prescribing information)[4] or whose BP is not adequately controlled with amlodipine (or another dihydropyridine calcium channel blocker [CCB]) alone or with valsartan (or another angiotensin II receptor blocker [ARB]) alone (US prescribing information).[5] This article provides a brief overview of the pharmacological properties of amlodipine/valsartan and reviews the clinical trial data for combinations of these antihypertensive agents. Medical literature on the use of amlodipine/valsartan in hypertension was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

Fixed-dose combinations of amlodipine/valsartan comprise antihypertensive agents with complementary mechanisms of action – a dihydropyridine CCB (amlodipine) and an ARB that acts selectively on the receptor subtype AT_1 (valsartan).[4] Both drugs have generally neutral effects on metabolic parameters such as blood lipid levels and insulin sensitivity,[6-8] and the association of antihypertensive drugs with the development of new-onset diabetes is lowest for ARBs and ACE inhibitors followed by CCBs,[9,10] whereas antihypertensive regimens that include a thiazide diuretic are among the most likely to be associated with the development of diabetes.[9,11]

The pharmacodynamic properties of amlodipine[12] and valsartan[13,14] have been reviewed previously in some detail; therefore, this section focuses on newer data specifically with combinations of amlodipine/valsartan. Some of these pharmacodynamic studies are available as abstracts,[15,16] although one is fully published.[17]

- Plasma noradrenaline levels in patients with mild to moderate hypertension (mean sitting diastolic BP [DBP] >95 and <110 mmHg) were increased by amlodipine but not valsartan monotherapy both at rest and while standing; however, combined therapy with amlodipine/valsartan did not attenuate the amlodipine-induced sympathetic activation.[17] Both drugs provided similar reductions in BP; therefore, results suggest that valsartan has a neutral effect on the sympathetic system despite achieving significant antihypertensive effects. During the first 4 weeks of the randomized, double-blind, forced-titration study, 47 patients received monotherapy with either amlodipine 5 mg or valsartan 80 mg once daily, which was increased to amlodipine 10 mg or valsartan 160 mg once daily through week 8. Patients whose DBP remained >90 mmHg at week 8 were treated with both drugs.
- As well as significantly reducing BP, the addition of valsartan 80 mg/day to amlodipine 5 mg/day in hypertensive patients with an inadequate response to amlodipine monotherapy also improved exercise performance, as assessed by measurements of cardiac output and total peripheral resistance at rest, after warm-up and at peak exercise.[15]
- Over a 1-year period, the combination of amlodipine/valsartan 10 mg/160 mg once daily was associated with a significantly lower rate of recurrent episodes of atrial fibrillation than amlodipine/atenolol 10 mg/100 mg once daily in a randomized study in 250 patients with mild hypertension, well controlled type 2 diabetes and a recent history of atrial fibrillation.[16] Although reductions in BP were similar between groups, 14% of patients treated with

1 The use of trade names is for product identification purposes only and does not imply endorsement.

amlodipine/valsartan experienced ≥1 recurrent episode of symptomatic or asymptomatic, ECG-documented atrial fibrillation compared with 41% of those who received amlodipine/atenolol ($p < 0.01$).

2. Pharmacokinetic Profile

Amlodipine and valsartan exhibit linear pharmacokinetic properties and the pharmacokinetic profiles of these drugs, when administered as monotherapy, are well defined.[4,12,13] Limited data are available on the pharmacokinetics of fixed-dose combinations of amlodipine/valsartan.[4,5]

- Peak plasma concentrations of amlodipine and valsartan are reached in 6–8 hours and 3 hours, respectively, following oral administration of amlodipine/valsartan in fixed-dose combinations.[4,5] The rate and extent of absorption of amlodipine when administered in fixed-dose combinations with valsartan are equivalent to those of amlodipine when administered as monotherapy. Likewise, valsartan has similar absorption pharmacokinetics whether administered in fixed-dose combinations with amlodipine or as monotherapy.
- When administered as individual components, amlodipine and valsartan have absolute bioavailabilities of 64–80% and 23%, respectively.[4] Both drugs are highly plasma protein bound and the elimination half-life is 30–50 hours for amlodipine and 6 hours for valsartan.
- Amlodipine is extensively (≈90%) metabolized in the liver to inactive metabolites, whereas only ≈20% of a valsartan dose is recovered as metabolites.[4,5] Valsartan is primarily eliminated in the faeces (≈83% of a dose) and urine (≈13% of a dose) mainly as unchanged drug.
- Both amlodipine and valsartan are associated with drug interactions of potential clinical significance[4,5] and local prescribing information should be consulted. No drug interaction studies have been conducted with fixed-dose combinations of amlodipine/valsartan and other drugs.

3. Therapeutic Efficacy

Several large, well designed clinical trials in patients with hypertension and/or other cardiovascular conditions have demonstrated reductions in morbidity and mortality with amlodipine[3,18-21] or valsartan.[22-26] To date, clinical trials with combinations of amlodipine/valsartan have focused on BP control, as discussed in the following three subsections. None of the studies conducted thus far have evaluated home or 24-hour BP or focused specifically on patients with isolated systolic hypertension.

Randomized Factorial Studies 1 and 2

The antihypertensive efficacy of combination therapy with amlodipine/valsartan has been compared with that of amlodipine or valsartan monotherapy in two randomized, double-blind, placebo-controlled, factorial studies. These large trials, referred to as study 1 (n = 1911) and study 2 (n = 1250), have been published together in a single report;[27] subgroup analyses have been published separately.[28]

The main inclusion criterion for studies 1 and 2 was mild to moderate essential hypertension, defined as a mean sitting DBP ≥95 and <110 mmHg.[27] Studies 1 and 2 were of similar design, in that they included a 2-week washout period followed by a 2- to 4-week single-blind placebo run-in period then an 8-week active-treatment period with once-daily oral administration of study medication. However, patients in study 1 could be randomized to receive 1 of 15 different regimens, whereas only six regimens were evaluated in study 2. Also, the amlodipine dose used in study 2 (10 mg) was higher than that used in study 1 (2.5 or 5 mg). Regimens in study 1 that involved low doses of amlodipine (2.5 mg) or valsartan (40 mg) are not included in this section; only combined amlodipine/valsartan dosages approved in the EU or commercially available in the US (section 5) are discussed.

The primary efficacy endpoint of studies 1 and 2 was the change from baseline in mean sitting DBP at the end of the 8-week study period in the intent-to-treat (ITT) population.[27] Important secondary end-

points were response rate, defined as the percentage of patients achieving a mean sitting DBP <90 mmHg or a ≥10 mmHg reduction from baseline, and change from baseline in mean sitting systolic BP (SBP). The overall mean age was 54.4 years in study 1, with 18.2% of patients aged ≥65 years, and 56.9 years in study 2, with 28.6% of patients aged ≥65 years. Baseline overall mean sitting BP values in the respective studies were 152.8/99.3 mmHg and 156.7/99.1 mmHg.

- After 8 weeks of treatment with amlodipine/valsartan 5 mg/80 mg, 5 mg/160 mg or 5 mg/320 mg once daily in study 1, reductions from baseline in mean sitting DBP (−14.2 to −15.9 mmHg) were significantly ($p < 0.05$) larger than with the same doses of amlodipine (−11.5 mmHg) or valsartan (−9.7 to –13.4 mmHg) monotherapy, or with placebo (−6.8 mmHg).[27]
- Reductions from baseline in mean sitting SBP in study 1 ranged from −19.5 to −22.7 mmHg with amlodipine/valsartan 5 mg/80 mg, 5 mg/160 mg or 5 mg/320 mg once daily and were significantly ($p < 0.05$) larger than those observed with amlodipine (−15.1 mmHg) or valsartan (−12.9 to −15.7 mmHg) monotherapy, or with placebo (–6.7 mmHg).[27]
- More than 80% of patients treated with amlodipine/valsartan 5 mg/80 mg (84.9%), 5 mg/160 mg (81.1%) or 5 mg/320 mg (91.3%) in study 1 met the criteria for response.[27] Response rates were significantly ($p < 0.05$) greater than that with placebo (40.9%). In addition, amlodipine/valsartan combinations achieved significantly higher response rates than amlodipine (71.9%) and/or valsartan (57.7–73.4%) monotherapy.
- In study 2, reductions from baseline in mean sitting DBP were significantly ($p < 0.05$) greater after 8 weeks of therapy with amlodipine/valsartan 10 mg/320 mg (–18.6 mmHg) or amlodipine/valsartan 10 mg/160 mg (–17.6 mmHg) once daily than with the same dose of amlodipine (–15.6 mmHg) or valsartan monotherapy (–13.3 mmHg for both 160 and 320 mg), or with placebo (–8.8 mmHg).[27]
- Reductions from baseline in mean sitting SBP in study 2 were approximately −28 mmHg with either combined regimen of amlodipine/valsartan and were significantly ($p < 0.05$) greater than those observed with amlodipine (−24.1 mmHg) or valsartan (approximately −20 mmHg for both 160 and 320 mg) monotherapy, or with placebo (−12.9 mmHg).[27]
- Almost 90% of patients treated with amlodipine/valsartan 10 mg/320 mg (87.5%) or 10 mg/160 mg (88.5%) in study 2 met the criteria for response.[27] In both cases this was significantly ($p < 0.05$) greater than the response rate with the same doses of valsartan monotherapy (72% or 74.9%) or with placebo (49.3%), although there was little difference in response rates between the combined regimens and amlodipine 10 mg monotherapy (86.9%).
- Subgroup analyses of studies 1 and 2, conducted according to the stage of hypertension, age and race, showed that changes from baseline in mean sitting DBP and SBP in the various subgroups were consistent with findings from the overall study population.[28] The combination of amlodipine/valsartan was associated with numerically greater reductions in BP than with each respective monotherapy or placebo across all patient subgroups evaluated, including elderly (≥65 years of age) and Black patients, as well as those with stage 2 hypertension (SBP ≥160 mmHg and/or DBP ≥100 mmHg). Statistical analyses were not reported.

Phase IIIb–IV (Direct Switch) Study

A large (n = 894), randomized, double-blind, phase IIIb–IV trial evaluated a direct switch (without washout) to amlodipine/valsartan 5 mg/160 mg or 10 mg/160 mg once daily in patients whose BP was previously uncontrolled with monotherapy (various antihypertensive agents).[29] BP control was defined as SBP/DBP <140/90 mmHg for nondiabetic patients and <130/80 mmHg for patients with diabetes. For patients with uncontrolled BP after 8 or 12 weeks of amlodipine/valsartan therapy, open-label hydrochlorothiazide (HCTZ) 12.5 mg/day could be added; for patients who received concurrent HCTZ 12.5 mg/day starting at week 8 and whose BP remained uncontrolled at week 12, the dose of HCTZ could be increased to 25 mg/day. The

primary endpoint was the proportion of patients achieving BP control at week 16; BP control at week 8 (i.e. prior to the possible addition of HCTZ) was an important secondary endpoint. The mean overall age of the study population was 58.5 years, with 30.6% aged ≥65 years.

- BP control was achieved in 76.4% and 71.1% of patients (p = 0.03) after 8 weeks of once-daily therapy with amlodipine/valsartan 10 mg/160 mg and 5 mg/160 mg, respectively (ITT with last observation carried forward [LOCF]).[29] During the subsequent 8-week period, HCTZ could be added if necessary, and results at week 16 were similar to those at week 8, although the difference between groups was not statistically significant (74.8% for amlodipine/valsartan 10 mg/160 mg vs 72.7% for amlodipine/valsartan 5 mg/160 mg), possibly because more patients in the low-dose group than in the high-dose group received HCTZ (25% vs 19%). In general, results were similar between nondiabetic and diabetic patients.
- At week 8, reductions in mean sitting SBP/DBP were −19.2/−11.3 mmHg with amlodipine/valsartan 10 mg/160 mg and −16.5/−9.3 mmHg with the lower dosage ($p \leq 0.0001$ for SBP and DBP comparisons; ITT with LOCF).[29] Similar results were reported at week 16 (−20.0/−11.6 mmHg vs −17.5/−10.4 mmHg; $p < 0.001$ for SBP, $p < 0.01$ for DBP).
- Week 8 data for reductions in mean sitting SBP (ITT without LOCF) are presented in figure 1.[29] In the lower-dosage group, the reduction in SBP was −17.6 mmHg, from 149.5 mmHg at baseline to 131.9 mmHg at week 8 (figure 1a). Amlodipine/valsartan 10 mg/160 mg was associated with a reduction of −21.0 mmHg, from 150.8 mmHg at baseline to 129.8 mmHg at week 8 (figure 1b). For both dosage regimens, the magnitude of SBP reductions was similar regardless of the class of antihypertensive drug used prior to randomization.

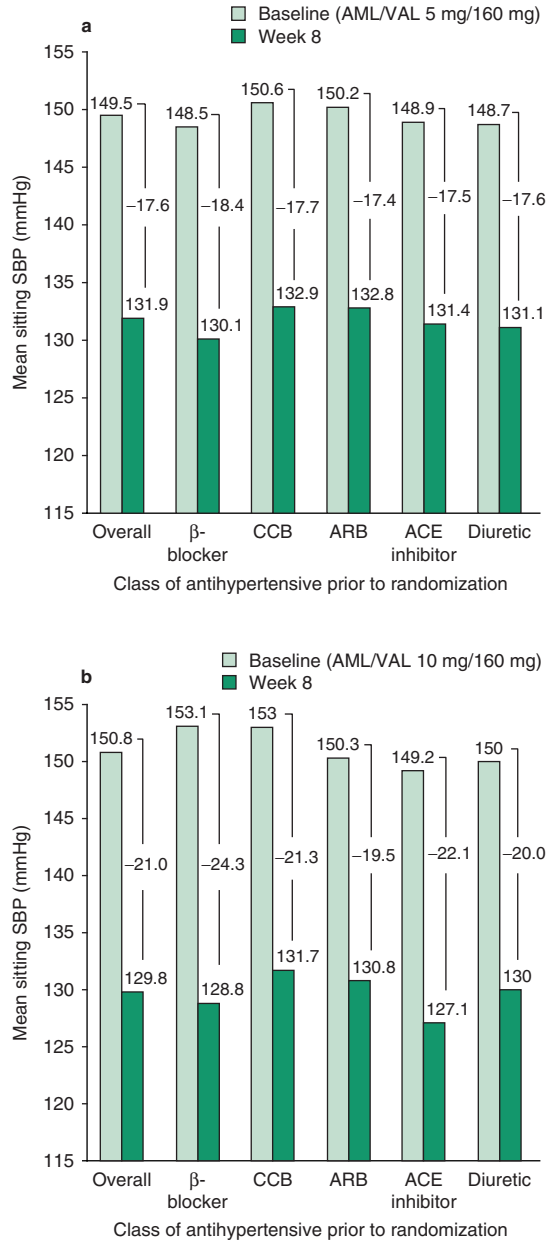

Fig. 1. Mean sitting systolic blood pressure (SBP) at baseline and 8 weeks after switching (without washout) to amlodipine/valsartan (AML/VAL) in a randomized, double-blind, phase IIIb-IV trial.[29] Hypertensive patients with previously uncontrolled blood pressure with antihypertensive monotherapy were switched (without washout) to (**a**) AML/VAL 5 mg/160 mg (n = 423) or (**b**) AML/VAL 10 mg/160 mg (n = 410) once daily. **ARB** = angiotensin II receptor blocker; **CCB** = calcium channel blocker.

Other Studies

Additional efficacy data are also available from two smaller comparative trials whose primary aim was to evaluate tolerability data.[30,31] Study design

details and primary safety data for these two studies are presented in section 4.

- Amlodipine/valsartan was associated with significant ($p < 0.001$) reductions in mean sitting SBP in the overall patient population (−35.8 mmHg), and in patients with mean sitting SBP ≥180 mmHg at baseline (−43.0 mmHg) in a 6-week trial comparing the tolerability profiles of once-daily regimens of amlodipine/valsartan 5–10 mg/160 mg and lisinopril/HCTZ 10–20 mg/12.5 mg in patients with stage 2 hypertension.[31] Significant ($p < 0.001$) reductions in DBP were also observed.
- Another 6-week study focusing on tolerability endpoints showed better antihypertensive efficacy with amlodipine/valsartan 10 mg/160 mg once daily than with amlodipine or valsartan monotherapy at the same dosages.[30]

4. Tolerability

Tolerability data on the combined use of amlodipine/valsartan are available from two large, randomized, factorial trials in patients with mild to moderate hypertension (studies 1 and 2)[27] and a phase IIIb–IV trial involving switch therapy (see section 3 for study design details),[29] as well as from two smaller trials whose primary aim was to evaluate safety variables.[30,31]

One of the tolerability studies compared the effects of amlodipine/valsartan 10 mg/160 mg on ankle oedema with those of amlodipine or valsartan monotherapy at the same once-daily dosage for 6 weeks.[30] Ankle foot volume (AFV) and pretibial subcutaneous tissue pressure (PSTP) were blinded endpoints used as objective measures of ankle oedema. The open-label crossover study included 80 patients with grade 1 or 2 hypertension who were randomized to receive the three treatment regimens. Each crossover period was separated by a 2-week placebo period.

The other tolerability study compared the overall safety profile of amlodipine/valsartan 5–10 mg/160 mg with that of lisinopril/HCTZ 10–20 mg/12.5 mg once daily in 130 patients with stage 2 hypertension.[31] The randomized, double-blind trial included a washout period of 3–7 days followed by a 1- to 2-week placebo run-in period and then a 6-week active-treatment period.

None of the clinical trials with amlodipine/valsartan specifically excluded patients who could not tolerate amlodipine or valsartan. In studies 1 and 2, the total number of patients enrolled in the single-blind, placebo run-in phase of the trials was 2478 and 1407, respectively, whereas 1911 and 1250 patients entered the randomized phase of the two trials.[27] The most common reasons for discontinuation were administrative problems, antihypertensive therapy no longer required, abnormal laboratory values and withdrawal of consent.

- The combined safety population from studies 1 and 2 included 3155 patients with mild to moderate hypertension.[27] The most frequently reported adverse events with amlodipine/valsartan were peripheral oedema, headache, nasopharyngitis, upper respiratory tract infection and dizziness (figure 2).

- Patients receiving combined therapy with amlodipine/valsartan had a significantly lower incidence of peripheral oedema than those treated with amlodipine monotherapy (5.4% vs 8.7%; $p < 0.05$), but a higher incidence than those receiving valsartan monotherapy (2.1%; $p < 0.001$); the incidence in placebo recipients (3.0%) did not differ significantly from that in combination recipients.[27] The lower incidence of peripheral oedema in combination versus amlodipine monotherapy recipients was thought to result from a decrease in both arteriolar and venous resistance associated with the combination, whereas amlodipine would be expected to reduce arteriolar resistance only.

- The incidence of headache was significantly lower in patients receiving amlodipine/valsartan therapy than amlodipine monotherapy (4.3% vs 7.6%; $p < 0.01$), but no different to that seen with valsartan monotherapy (4.8%) or placebo (5.9%).[27]

- The overall incidence of adverse events reported with amlodipine/valsartan was similar to that reported for amlodipine (44.1% vs 45.7%), but significantly higher than that reported for valsartan (44.1% vs 39.8%; $p < 0.05$).[27] The incidence of adverse events leading to discontinuation of study drug was

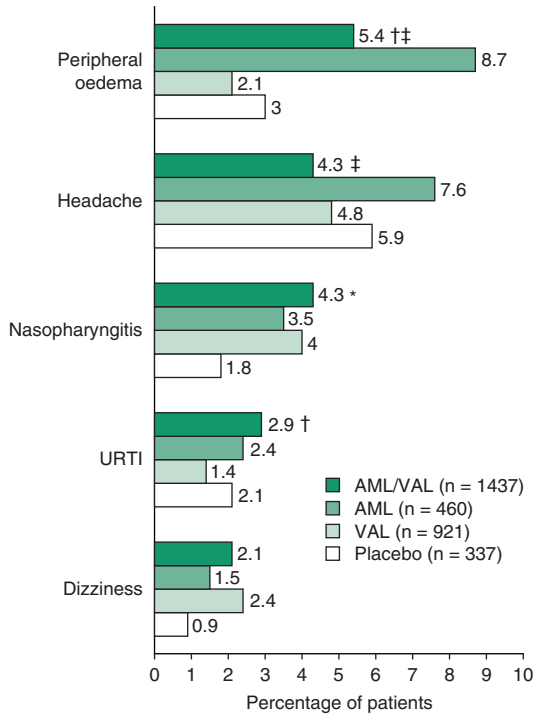

Fig. 2. Tolerability data from 3155 patients with mild to moderate hypertension. Pooled data from two randomized, double-blind, 8-week, factorial trials comparing combinations of amlodipine/valsartan (AML/VAL) vs monotherapy with either drug or placebo.[27] Adverse events are those reported in at least 2% of patients treated with AML/VAL. **URTI** = upper respiratory tract infection; * $p < 0.05$ vs placebo; † $p < 0.05$ vs VAL; ‡ $p < 0.05$ vs AML.

1.8% with amlodipine/valsartan, which was similar to that reported with placebo (2.1%).

- In the phase IIIb–IV trial in which patients with inadequate control of BP were switched (without washout) to amlodipine/valsartan 5 mg/160 mg or 10 mg/160 mg once daily for 16 weeks (with or without the addition of HCTZ at week 8 or 12), the most frequently reported treatment-related adverse event was peripheral oedema, which occurred in 8.1% and 25.1% of patients in the respective dosage groups.[29] Peripheral oedema led to discontinuation of therapy in 2.3% and 9.1% of patients, respectively.
- In the study evaluating ankle oedema in 80 patients, amlodipine/valsartan 10 mg/160 mg once daily for 6 weeks was associated with smaller increases from baseline in AFV (+6.8% vs +23%; $p < 0.01$) and PSTP (+23.2% vs +75.5%; $p < 0.001$) than amlodipine monotherapy.[30] These data also support the concept of reduced peripheral oedema with the dual mechanism of action of amlodipine/valsartan affecting arteries and veins. As expected, valsartan monotherapy did not affect AFV or PSTP.
- Amlodipine/valsartan 5–10 mg/160 mg or lisinopril/HCTZ 10–20 mg/12.5 mg once daily for 6 weeks were both generally well tolerated in 130 patients with stage 2 hypertension (DBP ≥110 mmHg and <120 mmHg) who participated in a randomized, double-blind trial.[31] Overall, adverse events were reported in 40.6% of patients treated with amlodipine/valsartan and 31.8% of those who received lisinopril/HCTZ. Most adverse events were mild to moderate in severity. Headache (10.9%) and peripheral oedema (7.8%) were the most frequently reported adverse events among amlodipine/valsartan recipients, whereas diarrhoea and pharyngitis (both 6.1%) were the most frequently reported adverse events with lisinopril/HCTZ.

5. Dosage and Administration

The recommended dose of amlodipine/valsartan for patients with hypertension in the EU is one tablet (5 mg/80 mg, 5 mg/160 mg or 10 mg/160 mg) once daily, taken with or without food.[4] In the US, commercially available dosages of amlodipine/valsartan include 5 mg/160 mg, 10 mg/160 mg, 5 mg/320 mg and 10 mg/320 mg, which are administered once daily.[5] Although a direct switch from monotherapy to the fixed-dose combination may be appropriate for some patients, individual dose titration with amlodipine and valsartan is generally recommended before changing to the fixed-dose combination.[4,5]

Caution is advised when prescribing the fixed-dose combination to patients with hepatic impairment or biliary obstructive disorders and when increasing the dosage of amlodipine/valsartan in elderly patients (>65 years of age).[4,5] The maximum recommended dose of valsartan is 80 mg in patients with mild to moderate hepatic impairment without cholestasis (EU prescribing information).[4] Dosage adjustments are not required for patients with mild

to moderate renal impairment, although potassium levels and serum creatinine should be monitored in those with moderate renal impairment.[4]

No specific drug interaction studies have been conducted with the fixed-dose combination of amlodipine/valsartan and other drugs, although interactions between the individual components (amlodipine or valsartan) and other drugs also apply to the fixed-dose combination.[4] Local prescribing information should be consulted for detailed information on drug interactions, contraindications, precautions and use in special patient populations.

6. Amlodipine/Valsartan: Current Status

Fixed-dose combinations of amlodipine/valsartan are available in several European countries for the treatment of patients with hypertension whose BP is not adequately controlled with amlodipine or valsartan monotherapy,[4] and in the US for patients whose BP is not adequately controlled with amlodipine (or another dihydropyridine CCB) alone or with valsartan (or another ARB) alone.[5] Individual dose titration with amlodipine and valsartan is generally recommended before changing to the fixed-dose combination.

Clinical trials have demonstrated that the combination of amlodipine/valsartan achieves greater reductions in BP than amlodipine or valsartan monotherapy in patients with mild to moderate hypertension, and the combination is associated with a significantly lower incidence of peripheral oedema than amlodipine monotherapy. Up to 90% of patients treated with approved dosage regimens of amlodipine/valsartan respond to short-term treatment, with DBP <90 mmHg or reductions of ≥10 mmHg after 8 weeks of therapy. Marked reductions in BP were also achieved in patients whose BP was previously uncontrolled on monotherapy (with various antihypertensives) who were switched (without washout) to amlodipine/valsartan. The combination of amlodipine/valsartan was generally well tolerated in clinical trials.

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