

Valsartan and amlodipine combination therapy for the treatment of hypertension

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Combination therapy with valsartan and amlodipine (Exforge) is used for the treatment of hypertension in patients who have not responded to monotherapy with either amlodipine or valsartan.

Studies have consistently shown that most patients with hypertension require two or more antihypertensive agents to control their blood pressure.^{1,2} This has led to the introduction of fixed-dose combination therapies that enable two antihypertensive drugs to be administered in the one tablet. These fixed-dose combinations, typically of ACE inhibitors or angiotensin receptor antagonists combined with diuretics, have become commonly used therapies in Australia because they offer the promise of greater patient acceptance and compliance than the individual drugs given alone. However, recent studies have suggested that either an ACE inhibitor or an angiotensin receptor antagonist combined with a calcium channel blocker may provide better blood pressure control and superior outcomes than combinations that contain a diuretic.^{3,4}

What is valsartan and amlodipine combination therapy?

Valsartan plus amlodipine (Exforge) is a fixed-dose combination, which consists of the angiotensin receptor antagonist valsartan and the dihydropyridine calcium antagonist amlodipine. It is available in the following strengths: amlodipine 5 mg with valsartan 80 mg or 160 mg (Exforge 5/80, 5/160), and amlodipine 10 mg with valsartan 160 mg (Exforge 10/160).

When is it used?

Combination therapy with valsartan and amlodipine has been approved by the TGA. It is available on the PBS (restricted benefit) for the treatment of hypertension in patients who have not responded to monotherapy with either amlodipine or valsartan. It is an effective alternative therapy to other fixed-dose dual antihypertensive regimens such as ACE or angiotensin receptor antagonist therapy combined with low-dose diuretics or calcium channel blockers.

How is it used?

Combination therapy with valsartan and amlodipine should not be used to initiate therapy. It should be used in patients who have been stabilised on individual tablets of amlodipine and valsartan. It can also be introduced as step-up therapy in patients who are receiving monotherapy with amlodipine (5 mg or 10 mg daily) or

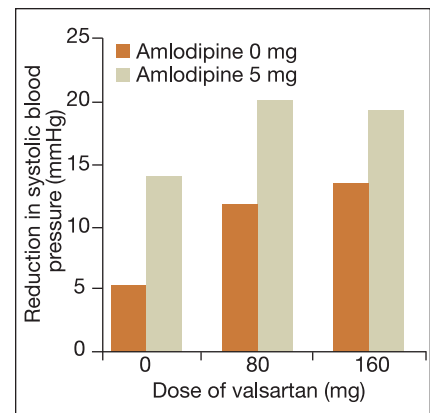


Figure 1. Additive effects of amlodipine 5 mg with valsartan 80 mg or 160 mg on the fall in systolic blood pressure.

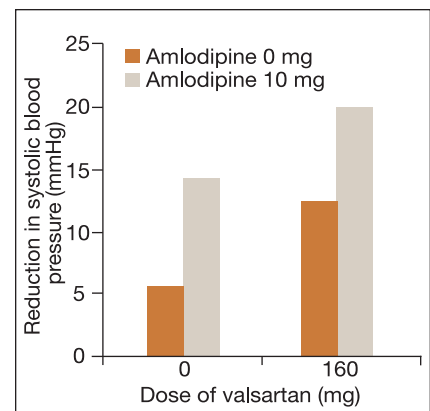


Figure 2. Additive effects of amlodipine 10 mg with valsartan 160 mg on the fall in systolic blood pressure.

valsartan (80 mg or 160 mg daily) in whom blood pressure remains uncontrolled. Patients who are not adequately controlled with valsartan therapy should initially receive combination therapy containing amlodipine 5 mg plus valsartan 80 mg. Patients who are not adequately controlled with amlodipine 5 mg plus valsartan 80 mg combination therapy should be titrated up to amlodipine 5 mg plus valsartan 160 mg per day. If blood pressure remains uncontrolled, titration up to amlodipine 10 mg plus valsartan 160 mg combination therapy should be performed.

This drug combination should be taken consistently prior to food consumption,

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along with food or following food. The timing of drug administration with respect to food does not matter but should remain constant in individual patients.

What is its efficacy

Valsartan and amlodipine have additive effects on blood pressure reduction throughout the range of the combinations available⁵ (Figures 1 and 2). The combination of amlodipine with valsartan has been shown to be superior to the combination of the ACE inhibitor lisinopril and the thiazide diuretic hydrochlorothiazide.⁶ The use of valsartan in combination with amlodipine has been shown to be associated with a lower incidence of ankle oedema than when amlodipine is used alone (5.8% *v.* 9%, respectively).⁶

What needs monitoring?

Blood pressure should be carefully monitored after the initiation of combination therapy with valsartan and amlodipine because significant hypotension and dizziness may occur. Renal function should be monitored within the first week of initiating therapy in patients who have not previously been receiving angiotensin receptor antagonist therapy because the use of these drugs in patients with bilateral or unilateral renal artery stenosis may cause acute renal failure. Serum potassium levels should be monitored because they may increase in patients receiving angiotensin receptor antagonists such as valsartan. Increases in serum potassium levels are particularly likely to occur in patients with renal impairment or diabetes, or in patients receiving NSAIDs, potassium or potassium-sparing diuretics.

Common side effects

Combination therapy with valsartan and amlodipine is generally well tolerated. Common side effects are those that are typical of the individual components of the combination therapy. The most frequently encountered side effects are headache and ankle oedema. Ankle oedema

typically occurs as a side effect of amlodipine therapy, although the incidence of this side effect is lower in patients taking combination therapy than amlodipine alone. Flushing may occasionally occur.

Precautions and drug interactions

Combination therapy with valsartan and amlodipine should not be used in patients with severe liver impairment because both drugs are eliminated principally by hepatic metabolism. Patients with mild to moderate liver impairment should not exceed a dose of amlodipine 5 mg plus valsartan 80 mg. Combination therapy with valsartan and amlodipine is safe to use in patients with mild to moderate renal impairment without the need for dosage adjustment, but it should not be used in patients with severe renal impairment or patients receiving dialysis. It should be taken consistently with respect to meals because food can influence the bioavailability of valsartan.

Combination therapy with valsartan and amlodipine should be used with caution in patients with mild to moderate hepatic impairment and in patients with known renal artery stenosis as excessive blood pressure reduction may occur and, in the case of patients with renal artery stenosis, an increase in serum creatinine levels may theoretically occur. The combination drug should also be used with caution in patients who are volume depleted.

Significant drug interactions may occur with drugs that inhibit cytochrome P450 (CYP 3A4), because CYP3A4 inhibitors may increase plasma levels of amlodipine. The full product information should be referred to for comprehensive documentation of side effects, precautions, contraindications and drug interactions.

Summary

In summary, the fixed-dose combination of amlodipine and valsartan will be a useful option for patients who have uncontrolled hypertension on monotherapy. **MT**

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This article is for general information purposes only, and the full product information should be consulted before prescribing any of the mentioned medications.

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