

Exforge: ARB/CCB combination for better hypertension control

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KEY POINTS

- fixed-dose combination of valsartan and amlodipine
- available as valsartan/amlodipine 80mg/5mg (28, £16.44), 160mg/5mg (28, £21.66) and 160mg/10mg (28, £21.66) tablets
- licensed for the treatment of hypertension when monotherapy with either component does not achieve adequate control
- in trials lasting eight weeks, treatment with Exforge reduced blood pressure in patients with hypertension by more than monotherapy with either component drug
- the commonest adverse effect is peripheral oedema; in clinical trials, this was 1-2 per cent less frequent with Exforge than with amlodipine alone
- same cost as valsartan taken as monotherapy; UK guidelines endorse the use of fixed-dose combinations where there is no cost disadvantage



Exforge is a combination of the ARB valsartan and the CCB amlodipine to treat patients whose blood pressure is not controlled with either component. In our review, Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Professor McInnes comments on its role in hypertension.

It is now accepted that many patients with hypertension need to take at least two drugs to achieve target blood pressure (BP) of 140/90mmHg or less.¹ Initial therapy for patients younger than 55 should be with an ACE inhibitor or, if this is not tolerated, an angiotensin-II receptor blocker (ARB); for older patients and black patients, the drug of first choice is a thiazide or a calcium channel blocker (CCB). When a second drug is needed, an ACE inhibitor or ARB should be added to a CCB or thiazide; and a CCB or thiazide should be added to an ACE inhibitor. Third-line therapy entails an ACE inhibitor/ARB, a CCB and a thiazide.¹

The rationale for prescribing antihypertensive drugs with different mechanisms of action is

that it offers a greater reduction in BP without the corresponding increased incidence of adverse effects that may occur by increasing the dose of monotherapy. Unfortunately, this strategy means that patients may have a greater number of tablets or containers to cope with every day, and this may impair adherence to treatment (particularly for patients also taking treatments for other cardiovascular risk factors). Fixed-dose combination products can reduce this burden and may therefore help to improve adherence.

The technology

Exforge is a combination of the ARB valsartan (Diovan) and the CCB amlodipine for the treatment of hypertension in patients whose

BP is not adequately controlled on amlodipine or valsartan monotherapy. It offers a fixed-dose combination that may be indicated as second- or third-line therapy according to National Institute for Health and Clinical Excellence (NICE) management guidance.

Exforge is available in three strengths: amlodipine 5mg plus 80 or 160mg valsartan, and amlodipine 10mg plus 160mg valsartan. The recommended dose is one tablet per day. Each strength of Exforge is indicated when target BP is not achieved with monotherapy using the corresponding dose of one of the component drugs; Exforge 10/160 is also indicated when target pressure is not achieved with Exforge 5/160. Ideally, the dose of each

Group	Baseline (mmHg)	Mean change from baseline	95% CI for change	p-value
Valsartan vs Exforge				
val/aml 160/10mg	96.6	-11.4	-12.13, -10.64	<0.0001
val/aml 160/5mg	96.8	-9.6	-10.47, -8.82	<0.0001
val 160mg	96.2	-6.6	-7.40, -5.74	<0.0001
Amlodipine vs Exforge				
val/aml 160/10mg	94.8	-11.8	-12.50, -11.06	<0.0001
aml 10mg	95.3	-10.0	-10.73, -9.26	<0.0001

Table 1. Reduction in blood pressure with Exforge, and valsartan and amlodipine monotherapy

component should be titrated separately but a direct switch from monotherapy to combined therapy is also licensed.

Clinical trials

Evidence for the efficacy of valsartan/amlodipine as second-line therapy comes from two (unpublished) pivotal randomised trials in patients with mild to moderate hypertension (mean baseline diastolic pressure 94-97mmHg).^{3,4} In one, 947 patients underwent four weeks' treatment with valsartan 160mg/day, and were then randomised to continue monotherapy or switch to treatment with valsartan/amlodipine 160/5mg or 160/10mg for eight weeks. In the second, 944 patients underwent four weeks' treatment with amlodipine 10mg/day, and were then randomised to continue monotherapy or switch to valsartan/amlodipine 160/10mg for eight weeks.

Compared with baseline, the mean reduction in diastolic pres-

sure after 12 weeks' treatment with valsartan monotherapy was 6.6mmHg; this was significantly less than with valsartan/amlodipine (9.6mmHg for 160/5mg and 11.4mmHg for 160/10mg, see Table 1). For amlodipine monotherapy, the mean reduction in diastolic pressure was 10mmHg, significantly less than with valsartan/amlodipine 160/10mg (11.8mmHg).

The proportions of patients in whom diastolic pressure was reduced below 90mmHg were 53 per cent with valsartan monotherapy, and 62 and 75 per cent respectively with valsartan/amlodipine 160/5mg and 160/10mg. For amlodipine monotherapy, this target was achieved in 67 per cent of patients compared with 78 per cent taking valsartan/amlodipine 160/10mg.

In 130 patients with severe hypertension (baseline BP 171/113mmHg),^{3,4} first-line treatment for six weeks with valsartan/amlodipine 160/5mg-160/10mg or

lisinopril/hydrochlorothiazide 10/12.5mg-20/12.5mg achieved similar reductions in diastolic (29 and 28mmHg respectively) and systolic (36 and 32mmHg) pressure. Target BP was achieved in 80 per cent of patients taking valsartan/amlodipine and 77 per cent of those taking lisinopril/hydrochlorothiazide.

Adverse effects

The adverse effects associated with valsartan/amlodipine are those of the component drugs. The incidence of peripheral oedema with the combination is slightly lower than with amlodipine alone (an absolute reduction in incidence of 1-2 per cent)⁴; this may be due to a direct microcirculatory effect of valsartan.⁵ In data pooled from clinical trials, the incidence of peripheral oedema with valsartan/amlodipine 80/5mg and 160/5mg was 2.3 and 2.1 per cent respectively; with 160/10mg it was 9 per cent (see Table 2).³

	Valsartan/amlodipine (mg)			Amlodipine (mg)			Placebo
	160/10 n (%)	160/5 n (%)	80/5 n (%)	10 n (%)	5 n (%)	2.5 n (%)	
Total population	999	512	128	677	128	125	337
Peripheral oedema	90 (9.0)	11 (2.1)	3 (2.3)	70 (10.8)	4 (3.1)	10 (8.0)	10 (3.0)

Table 2. Incidence of peripheral oedema with Exforge, amlodipine monotherapy and placebo

Summary

Exforge, a fixed-dose combination of valsartan and amlodipine, more effectively controls BP in patients with hypertension than either of its components given as monotherapy. The incidence of peripheral oedema was somewhat lower in the valsartan/amlodipine patients when compared to amlodipine alone.

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By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

Treatment of hypertension is often inadequate, with 60 per cent of treated individuals remaining hypertensive.¹ It has been estimated that if everyone with hypertension achieved target BP, 42 800 strokes and more than 82 000 coronary heart disease events would be prevented annually.²

Fixed-dose combinations appear more convenient and are more likely to be taken compared with free dose combinations, leading to increased likelihood of BP control.³ Thus, UK guidelines endorse the use of fixed-dose combinations where there are no cost disadvantages.⁴

Multiple pathways

Fixed-dose combinations that target multiple pathophysiological pathways would be expected to maximise BP lowering and reduce counter-regulatory mechanisms that would otherwise oppose BP reduction.

The action of CCBs on vascular smooth muscle reduces peripheral vascular resistance and thus BP. Consequent activation of the renin-angiotensin system (RAS) opposes the antihypertensive effect.⁵ ARBs

inhibit activation of the RAS, thereby maintaining the antihypertensive effects of CCBs. In addition, the natriuretic effect of CCBs further reinforces the antihypertensive effect of ARBs. Thus, in combination, amlodipine and valsartan have additive effects on BP. Furthermore, both drugs tend to reduce the incidence of new-onset diabetes,^{6,7} a frequent complication of therapy with diuretics and beta-blockers.

Amlodipine and valsartan are generally well tolerated. However, CCBs induce arterial but not venous dilatation, causing capillary overload that forces fluid into the surrounding tissue, resulting in oedema. ARBs dilate both arteries and veins, thus attenuating CCB-induced oedema by as much as 70 per cent despite greater BP reduction.⁸

Summary

Resistance to the use of fixed-dose combinations in the UK has been based on theoretical arguments, particularly that such formulations may magnify the risk of adverse events. The opposite may be the case if logical combinations are selected. If valsartan-amlodipine provides the early and rigorous control of BP predicted from clin-

ical trials, with fewer side-effects compared with other therapies, then worthwhile additional cardiovascular risk reduction can be expected.

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