

NEW DRUG EVALUATION

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ALISKIREN

Aliskiren is an orally active renin inhibitor licensed for the treatment of essential hypertension. In short-term studies it was effective in lowering blood pressure either alone or in combination with valsartan and hydrochlorothiazide and had a low incidence of serious adverse effects. Aliskiren is more expensive than most other antihypertensive agents and no long-term clinical outcome data are available. Its role in combination therapy has not been fully explored and there are no data on its use in severe hypertension. There is no evidence to support its use ahead of more established therapies in the treatment of hypertension. However, it may have a limited role as add-on therapy in patients who are poorly controlled on combinations of conventional antihypertensive agents.

What is it?

Aliskiren (Rasilez[®], Novartis), the first in a new class of orally active renin inhibitors, is licensed for the treatment of essential hypertension.¹ It inhibits plasma renin activity directly, thereby reducing generation of angiotensin II.¹ The recommended dose is 150mg once daily, which may be increased to 300 mg daily if blood pressure (BP) remains uncontrolled.¹

How effective is it?

A number of short-term, double-blind, randomised controlled trials have evaluated the antihypertensive efficacy and safety of aliskiren in patients with mild to moderate hypertension without any other associated conditions.²⁻⁶

An eight-week, multicentre, placebo-controlled study in 672 patients (mean BP 152/100 mm Hg) demonstrated significant reductions in BP at doses of 150, 300 and 600 mg ($p < 0.0001$).² Mean sitting diastolic BP was reduced from baseline by 10.3, 11.1 and 12.5 mm Hg and mean sitting systolic BP reduced by 13.0, 14.7 and 15.8 mm Hg (with 150, 300 and 600 mg respectively). No additional benefits from increasing the aliskiren dose from 300 mg to 600 mg were demonstrated.² Ambulatory monitoring in a subset of patients ($n = 216$), demonstrated a sustained 24-hour reduction in BP.²

A four-week trial ($n = 226$) comparing aliskiren with losartan demonstrated significant dose-dependent reductions in daytime ambulatory systolic BP with aliskiren 75, 150 and 300 mg ($p = 0.0002$). Losartan 100 mg demonstrated comparable reductions in ambulatory systolic BP to aliskiren 150 mg and 300 mg (11.4, 10.0 and 11.8 mm Hg, respectively).³ The reduction in diastolic BP with losartan 100 mg was comparable to that with aliskiren 300 mg (5.5 and 5.7 mm Hg, respectively).³

Aliskiren was compared with irbesartan in an eight-week trial ($n = 652$). Aliskiren 150 mg was as effective as irbesartan 150 mg in reducing sitting systolic (10.9 vs. 12.5 mm Hg) and diastolic (9.4 vs. 9.1 mm Hg) BP. Aliskiren 300 mg daily demonstrated a further reduction in sitting systolic (15.5 mm Hg) and diastolic (12.0 mm Hg) BP. However, additional benefits from increasing the dose to 600 mg were not shown.⁴

The use of valsartan and aliskiren in combination was assessed in an eight-week trial involving 1,797 patients. After dose titration aliskiren 300 mg and valsartan 320 mg were comparable in terms of the mean reduction in sitting diastolic (9.0 and 9.7 mm Hg, respectively) and systolic (13.0 and 12.8 mm Hg, respectively) BP. The combination of both agents reduced sitting diastolic (12.2 mm Hg) and systolic (17.2 mm Hg) BP significantly more than either agent alone ($p < 0.0001$).⁵

An eight-week placebo and active comparator trial ($n = 2,752$) assessed BP reductions with aliskiren and hydrochlorothiazide alone, and in combination (at varying doses). Significant reductions in mean sitting diastolic and systolic BP were demonstrated with aliskiren compared with placebo ($p \leq 0.0002$). Each of the combinations was superior to placebo ($p < 0.0001$) and most were superior to monotherapy with either agent ($p < 0.05$). The maximal mean reductions in diastolic (14.3 mm Hg) and systolic (21.2 mm Hg) BP observed with the combination of aliskiren 300 mg and hydrochlorothiazide 25 mg were significant when compared with the individual components alone.⁶

Another six-week study demonstrated the effects of adding aliskiren 150 mg to amlodipine 5 mg in a group of patients for whom amlodipine 5mg monotherapy was insufficient. The addition of aliskiren resulted in a further decrease in diastolic BP (8.5 mm Hg compared with 4.8 mm Hg for monotherapy, $p < 0.0001$). The benefits of adding aliskiren in this group were comparable with the group randomised to treatment with amlodipine 10 mg (decrease in diastolic BP of 8.0 mm Hg, $p = 0.0002$).⁷

Clinical trials assessing the effects of aliskiren compared to, and in combination with, Angiotensin Converting Enzyme (ACE) inhibitors and calcium channel blockers are planned. Evaluations of its use in a number of therapeutic areas (including heart failure, diabetes and post-MI) are also being conducted.⁸

How safe is it?

Aliskiren was well tolerated, with low discontinuation rates, in the study populations. The incidence of hyperkalaemia (serum potassium > 5.5 mmol/L) was low when aliskiren was used as monotherapy (2%).

In combination with valsartan, hyperkalaemia was more frequent (4%). Nevertheless, routine biochemical monitoring of electrolytes and renal function would be advisable.

Diarrhoea was the only adverse effect occurring significantly more frequently with aliskiren than placebo, and this was only in a subgroup receiving 600 mg aliskiren.² Angioedema has been reported rarely.¹ There is no information on the use of this agent in patients with severely impaired renal function.¹ As with other agents affecting the renin-angiotensin pathway, aliskiren is contraindicated in pregnancy and should be used with caution in women of childbearing age.¹ All suspected adverse reactions to black triangle drugs such as aliskiren should be reported to the MHRA via the Yellow Card Scheme (www.yellowcard.gov.uk).

What other options are there?

The National Institute for Health and Clinical Excellence, in conjunction with the British Hypertension Society, published detailed guidance for the management of hypertension in adults in primary

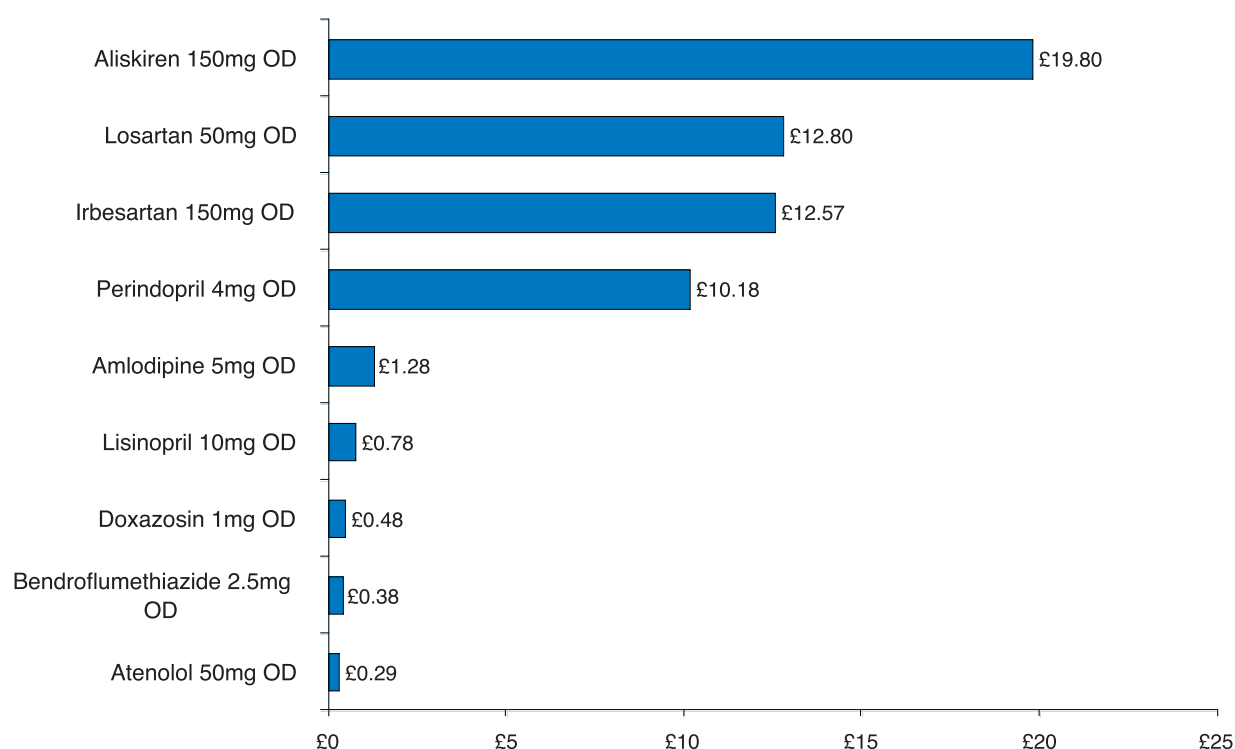
care.⁹ The recommendations state that thiazide diuretics or calcium channel blockers should be offered as first-line treatment for patients over 55 years of age and black patients of any age, and ACE inhibitors for patients under 55 years.⁹

When should it be used?

At present there is no convincing evidence to support the choice of aliskiren above other, more established agents. It has not been studied in combination with a number of these established agents, and its efficacy in severe hypertension is unknown. The benefits, if any, of inhibiting the renin-angiotensin pathway at an earlier stage than with ACE inhibitors and angiotensin receptor blockers are currently unclear. There are no long-term clinical outcome data with this agent which is expensive, compared to other available antihypertensive drugs. Many hypertensive patients require more than one agent to control BP and aliskiren may have a role as an add-on therapy in those uncontrolled using traditional treatment algorithms.

How much does it cost?

Cost of 28 days treatment (Drug Tariff/eMIMS February 2008)



N.B. Doses are shown for general comparison only and do not imply therapeutic equivalence. Further cost comparison charts can be found in the Prescribing Analysis and Report section of the RDTC website www.nyrdtc.nhs.uk/Services/presc_supp/presc_supp.html

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KEY RCT - randomised controlled trial, G - guideline

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