aliskiren 150mg and 300mg film-coated tablets (Rasilez®)

No. (462/08)

Novartis Pharmaceuticals UK Ltd

15 January 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

aliskiren (Rasilez®) is not recommended for use within NHS Scotland for the treatment of essential hypertension.

Aliskiren has shown comparable efficacy to other antihypertensive agents in terms of blood pressure reduction, though its effects on mortality and long-term morbidity are currently unknown.

The manufacturer did not present a sufficiently robust clinical or economic analysis to gain acceptance by the SMC for the position sought.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Essential hypertension.

Dosing information

The recommended dose of aliskiren is 150mg once daily. In patients whose blood pressure is not adequately controlled, the dose may be increased to 300mg once daily. Aliskiren may be used alone or in combination with other antihypertensive agents.

Product availability date

3 September 2007

Summary of evidence on comparative efficacy

Aliskiren inhibits the activity of renin, thereby inhibiting activation of the renin-angiotensin system at an earlier stage than angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor antagonists (ARA).

The submitting company has requested that the Scottish Medicines Consortium consider the use of this product in a sub-set of patients being treated for essential hypertension: patients reaching step 4 of the joint guidelines from the National Institute for Health and Clinical Excellence and the British Hypertension Society (NICE/BHS). The clinical data for this proposed niche will be presented later, but the following paragraphs give an overview of the antihypertensive efficacy of aliskiren based on clinical evidence from 15 clinical trials presented for European registration of this product.

All studies recruited patients with mild to moderate essential hypertension (except one small study in patients with uncomplicated severe hypertension) and exclusion criteria in all studies included the presence of a renal disorder, a secondary form of hypertension and conditions altering the pharmacokinetics of any medicinal product.

All studies were randomised and double-blind, parallel-group design and included a placebo run-in phase preceded by a washout period for patients who had been taking previous antihypertensive therapy. Some studies were dose-finding in the range 75mg to 600mg once daily, and all included at least one of the licensed doses of 150mg and 300mg aliskiren daily. The duration of active treatment was up to 26 weeks but was 8 weeks in eight studies. Studies investigating aliskiren in special groups involved patients with diabetes mellitus, obesity, and patients ≥65 years of age.

All studies recorded the change from baseline to endpoint in mean sitting diastolic and systolic blood pressures (msDBP and msSBP) and the primary end-point was DBP in 13 studies, ambulatory SBP in one study, and safety in another. These were analysed in the intention to treat (ITT) populations. Secondary endpoints included msSBP or msDBP (when each was not a primary endpoint), the proportion of patients with successful BP response and control and effects on plasma renin concentration and activity.

Aliskiren at doses of 150mg and 300mg provided dose-dependent reductions in both SBP and DBP that were maintained over the entire 24-hour dose interval, with 85% to 90% of the maximal BP lowering effect being observed after 2 weeks.

For example, statistically significant placebo-controlled reductions in msDBP over 8 weeks were in the range 2.0 to 5.4mmHg for 150mg aliskiren and 3.3 to 7.5mmgHg for 300mg. The equivalent ranges for msSBP were 4.8 to 9.3mmHg and 5.0 to 11.2mmHg respectively. The BP reductions were sustained during 26 weeks of treatment in three studies. The antihypertensive effect was independent of age, gender, body mass index and ethnicity. Aliskiren monotherapy in five studies has shown BP lowering effects comparable to other classes of antihypertensive agents including ACEi, ARAs, and the diuretic hydrochlorothiazide. For example, in the only study to show a significant difference between aliskiren and comparator for both msDBP and msSBP reduction, the difference between aliskiren 300mg and hydrochlorothiazide 25mg at 12 weeks was 2.0mmHg for msDBP and 2.8mmHg for msSBP.

Aliskiren was studied in combination with hydrochlorothiazide, ARA, ACEi, calcium channel blocking drugs (CCB) and beta-adrenergic blocking drugs. Combination therapy studies have shown additive BP-lowering effects of aliskiren compared to the corresponding monotherapies, although the difference was not consistently significant. For example, aliskiren in combination with valsartan showed an additive antihypertensive effect at 8 weeks, which was significant in one study comparing the combination with aliskiren monotherapy but not in another study comparing it with valsartan monotherapy. In the first study the difference in BP reduction between aliskiren 300mg/valsartan 320mg and aliskiren alone was 2.7mmHg for msDBP and 4.4mmHg for msSBP. In the second study the non-significant difference in msDBP reduction was 1.1mmHg comparing aliskiren 150mg/valsartan 160mg with valsartan alone and 1.7mmHg for aliskiren 300mg/valsartan 320mg versus valsartan. The equivalent differences for msSBP reduction were 1.1mmHg and 1.5mmHg respectively. In one study in diabetic hypertensive patients, aliskiren 300mg provided significant additive BP reductions when added to ramipril 10mg (2.1mmHg for msDBP and 4.6mmHg for msSBP). Combination studies have also demonstrated comparable efficacy for aliskiren compared with a second agent when both were combined with a third agent.

Evidence to support the proposed niche for aliskiren at step 4 of NICE/BHS guidelines comes from two observational studies which surveyed General Practitioners who had prescribed aliskiren. An abstract report of the first study includes details of 67 patients with uncontrolled BP (>140/90mm Hg) despite treatment with an ACEi/ARA, calcium channel blocker (CCB) plus a thiazide-type diuretic and indicates that 12 weeks of additional treatment with aliskiren 150mg daily reduced SBP/DBP by 16.2/9.9mm Hg (from baseline of 166.1/93.1 to 146.2/81.7mm Hg). In patients who had the aliskiren dose titrated to 300mg daily, BP was reduced by 22.4/9.6mm Hg over 12 weeks (from baseline of 174.6/94.8 to 151.9/81.6mm Hg). The company also performed a separate analysis in 135 patients who were at step 4 of NICE/BTS guidelines and received aliskiren 150mg daily. After 12 weeks, SBP/DBP reduced by 16.2/8.9mmHg (from baseline of 168.3/93.8mmHg).

The second study, conducted by the manufacturer, asked for details of patients whose records indicated that they had been prescribed aliskiren for at least 4 weeks, having been tried on a representative drug from all classes of therapy recommended in steps 1 to 3 of the NICE/BHS guidelines and, despite this, required addition of, or substitution with, a fourth-line agent. The authors concluded that, over 4 weeks, aliskiren 150mg daily achieved a mean reduction in SBP of 17.2mmHg in 90 patients and 15.7mmHg with 300mg aliskiren daily in 26 patients.

Summary of evidence on comparative safety

The European Medicines Agency's (EMEA) European Public Assessment Report (EPAR) describes a pooled analysis of safety data obtained in a total of 11,566 treated patients including 7,896 who received at least one dose of aliskiren, 2,367 who were exposed to aliskiren for 6 months and 1,270 exposed for 12 months. The safety population consisted of adults with mild to moderate essential hypertension with the exception of one study (severe essential hypertension). Common adverse events (AEs) included diarrhoea, cough, peripheral oedema, fatigue, rash, and influenza. Diarrhoea was the most common AE though the incidence was low at doses up to 300mg. Cough was the second most common AE but was substantially less frequent in patients treated with aliskiren than in patients treated with ACEi (1.0% versus 3.8%). Peripheral oedema was substantially less frequent in patients treated with aliskiren than in patients treated with amlodipine (0.9% versus 7.3%).

The incidence of serious AEs was similar for aliskiren and placebo. Increases in serum potassium were minor and infrequent in patients with essential hypertension treated with aliskiren alone. However, in one study where aliskiren was used in combination with an ACEi in a diabetic population, increases in serum potassium were more frequent. Therefore as with any agent acting on the renin-angiotensin system, routine monitoring of electrolytes and renal function is indicated in patients with diabetes mellitus, kidney disease or heart failure.

A recent Drug Safety Update from the Medicines and Healthcare products Regulatory Agency and the Commission on Human Medicines in May 2009 issued advice on aliskiren and the risk of angioedema and renal failure.

Summary of clinical effectiveness issues

Change in blood pressure was investigated in line with EMEA guidance during the aliskiren clinical programme, but it is recognised that change in blood pressure is a surrogate endpoint in such studies. In none of the aliskiren studies were mortality or morbidity data analysed, or target organ damage assessed.

The main clinical programme supports the antihypertensive efficacy of aliskiren as monotherapy and in combination with other antihypertensive agents, predominantly in patients with mild to moderate hypertension. In general, efficacy was comparable to the alternative treatment regimens studied. Aliskiren offers the potential advantage of a longer half-life (40 hours) than many other antihypertensives.

The submitting company has requested that aliskiren be considered for use in a sub-set of patients at step 4 of NICE/BHS guidelines i.e. for patients that remain uncontrolled having been titrated to the maximum tolerated dose of a representative drug from all classes of therapy recommended in steps 1-3 of the NICE/BHS guidelines. The main clinical trial programme provides no specific data for patients at this stage of treatment. Patients at step 4 are more likely to have severe, treatment resistant hypertension and are unlikely to reflect the patient population studied in the clinical trial programme in which all but one study recruited patients with mild to moderate hypertension.

The company has therefore presented the results of two observational studies in which prescribers in primary care were asked for data on patients who had been prescribed

aliskiren for 4 weeks or more and whose prescribing history indicated that the patient had been treated with three classes of drug at some stage.

However no details are provided on existing or previous antihypertensive therapies or the definition of maximal tolerated doses making it difficult to determine whether background therapy was optimised. It is not clear how prescribers were selected to participate in these studies and whether such 'early adopters' and their patients are representative of clinical practice. In addition, the methods of BP measurement may not have been as rigorous and consistent as would be expected in controlled trials.

The submission provided no comparison (direct or indirect) with other step 4 agents e.g. alpha-blockers, beta-blockers, spironolactone, although it is acknowledged that the evidence supporting these agents at step 4 is limited.

Summary of comparative health economic evidence

The manufacturer developed a 30-year cost-utility Markov model with a 6-monthly cycle to estimate the effects of hypertension upon cardiovascular events. Arms in the model were differentiated by the effect of the addition of aliskiren or placebo on patients' systolic blood pressure. Other treatments were not considered, despite the stated position sought by the manufacturer as being an alternative option at step 4.

The model was largely based upon the Framingham equations, with cost and utility values for the various health states being sourced mainly from the NICE hypertension guideline. Diabetes was also modelled through a sub-set of the United Kingdom Prospective Diabetes Study (UKPDS) risk equations, with an annual incidence of diabetes estimate being drawn from NICE guidance.

The effect of aliskiren on systolic blood pressure in the base case (a reduction of 16.2mmHg) was taken from 12-week data of an uncontrolled observational study, with 29% of this patient population having type 2 diabetes. The base case assumed that there would be no change in systolic blood pressure in the comparator arm. A scenario analysis applied the placebo effect upon systolic blood pressure (a reduction of 8.7mmHg) from a separate study in step 4 patients to the comparator arm.

The base case estimate was that aliskiren would cost an additional £2,226 per patient and provide an additional 0.183 QALYs, to yield a cost-effectiveness estimate of £12,142 per QALY.

The scenario analysis with a placebo effect estimated that aliskiren would cost an additional £2,453 per patient and provide an additional 0.085 QALYs, to yield a cost-effectiveness estimate of £28,801 per QALY. Additional information supplied by the manufacturer indicated that in the non-diabetic population the cost-effectiveness was estimated to be £36,093 per QALY, whilst in the diabetic population the cost-effectiveness was estimated to be £23,029 per QALY.

Base case results were sensitive to the effect upon systolic blood pressure: if this reduced by less than 7.3mmHg the cost-effectiveness rose to more than £30,000 per QALY. Results were particularly sensitive to the time horizon adopted, which may question the validity of an assumption that the impact on systolic blood pressure will be maintained throughout the patient lifetime.

Weaknesses of the analysis related primarily to the quality of the clinical evidence.

Additional weaknesses included:

- not considering other treatments possible at step 4 as comparators (although it is acknowledged that the evidence supporting these agents is limited);
- the base case assuming no placebo effect when a reasonable placebo effect in step 4 patients had been identified within the literature;
- not exploring the possibility of the effect on SBP not being maintained over the 30 year time horizon;
- undertaking a de novo modelling exercise for diabetes when there are well established and validated models for this sub-group, and,
- not considering those with diabetes and those without diabetes as separate sub-groups.

Given these issues, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by the SMC for the position sought.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Guidelines developed jointly by NICE and BHS were updated in August 2006. They group together ACEi and ARAs as class A, thiazide-like diuretics as class D, and calcium channel blockers (CCBs) as class C. They provide a treatment algorithm for escalation through those classes at step 1 (one class), step 2 (two classes) and step 3 (three classes). At step 4, for patients who do not meet BP targets at step 3, the guidelines recommend the addition of further diuretic therapy (increasing the dose of thiazide diuretic with careful monitoring or adding alternatives such as spironolactone or amiloride), a selective alpha adrenergic blocker or a beta adrenergic blocker.

Additional information: comparators

The submitting company is asking the Scottish Medicines Consortium to consider the use of aliskiren at step 4 of NICE / BHS guidelines for patients who have failed to respond to at least three other agents and who require additional therapy. In this scenario the alternative option is to continue with previous treatment, with the addition of further diuretic therapy (increasing the dose of thiazide diuretic with careful monitoring or adding alternatives diuretics), a selective alpha-adrenergic blocker or a beta-adrenergic blocker.

Cost of relevant comparators

The submitting company is asking the Scottish Medicines Consortium to consider the use of aliskiren at step 4 of NICE / BHS guidelines for patients who have failed to respond to at least three other agents and who require additional therapy. In this scenario the alternative option is to continue with previous treatment unchanged with the addition of further diuretic therapy, a selective alpha-adrenergic blocker or a beta-adrenergic blocker. Loop diuretics are not specifically mentioned in NICE / BHS guidelines but are licensed for resistant hypertension.

Within each class, the individual agents have been chosen to represent the most frequently prescribed within that class.

Drug	Dose regimen (all oral)	Cost per year (£)
Aliskiren	**150mg to 300mg once daily**	**257 to 309**
Potassium-sparing diuretics		
Amiloride	5mg to 10mg once daily	13 to 26
Spironolactone*	100mg to 400mg daily	41 to 166
Alpha adrenergic blocking drugs		
Doxazosin	2mg to 16mg once daily	12 -76
Indoramin	25mg to 100mg twice daily	78 to 312
Beta adrenergic blocking drugs		
Atenolol	25mg to 50mg once daily	12
Bisoprolol	10mg to 20mg once daily	16 to 33
Loop diuretics		
Furosemide	40mg to 80mg once daily	12 to 23

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 and 27 November 2009.

* NB Spironolactone is not licensed for the treatment of hypertension

The costs of drugs affecting the renin-angiotensin system are given below for information, though these are not comparators in the niche being sought. Within each class, the individual agents have been chosen to represent the most frequently prescribed within that class.

Drug	Dose regimen (all oral)	Cost per year (£)
Aliskiren	**150mg to 300mg once daily**	**257 to 309**
Angiotensin-converting enzyme inhibitors		
Ramipril	2.5mg to 10mg once daily	14 to 19
Enalapril	20mg to 40mg once daily	17 to 33
Lisinopril	20mg to 80mg once daily	17 to 66
Perindopril	2mg to 8mg once daily	30 to 33
Angiotensin II receptor antagonists		
Candesartan	8mg to 32mg once daily	129 to 210
Irbesartan	150mg to 300mg once daily	157 to 211
Losartan	50mg to 100mg once daily	166 to 210

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 and 27 November 2009.

Additional information: budget impact

The manufacturer estimated that around 45,000 patients are currently treated with step 4 therapy and eligible for aliskiren, and that this would rise to 55,000 by year 5. Given assumed market shares of 3.2% in year 1 rising to 10% by year 5, this resulted in 1,464 patients receiving aliskiren in year 1 rising to 5,520 by year 5.

The manufacturer estimated a gross drug cost of £397k in year 1, rising to £1.5m by year 5. There would be no direct cost offset to this due to aliskiren being additional to current therapy.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including ***04 December 2009.***

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. The references shaded grey are additional to those supplied with the submission.

Williams B, Lacy PS, Stanley AG. PA.2. Blood pressure lowering efficacy of direct renin inhibiton (aliskiren) in resistant hypertension – an observational study from UK primary care. Journal of Human Hypertension 2009; 23(Suppl 1):S10.

European medicines Agency (EMEA) European Public Assessment Report (EPAR) for aliskiren (Rasilez®), EMEA/H/C/780/II/26 www.emea.europa.eu

Medicines and Healthcare products Regulatory Agency. Drug Safety Update 2009; 2: issue 10

British Hypertension Society (BHS) Therapeutic Guides: Direct Renin Inhibitors, date accessed 16 September 2009.