

**aliskiren, 150mg and 300mg film-coated tablets (Rasilez<sup>®</sup>)**  
**No. (462/08)**

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**Novartis Pharmaceuticals UK Ltd**

05 December 2008

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 full submission

**aliskiren (Rasilez<sup>®</sup>)** 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 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<sup>rd</sup> 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) and who are unresponsive to other agents and/or for whom there are no suitable alternatives. 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  $\geq 65$  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 diastolic BP 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 systolic and diastolic BP that were maintained over the entire 24-hour dose interval, with 85-90% 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 7.5mmHg 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 long-term treatment. 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. Effects of aliskiren on mortality, cardiovascular morbidity, and target organ damage are currently unknown.

Evidence to support the proposed niche for aliskiren at step 4 of NICE/BHS guidelines comes from two observational studies, one of which surveyed GPs who had prescribed aliskiren while the other surveyed hospitals experienced in its use. Both asked for details of patients whose records indicated that they had been prescribed aliskiren for at least four weeks, had 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 four weeks, aliskiren 150mg achieved a mean reduction in systolic blood pressure of 17.25mmHg in 90 patients in primary care and 27mmHg in three hospital patients. The corresponding reductions with 300mg aliskiren were 15.7mmHg (n=26) and 11mmHg (n=19) respectively.

### **Summary of evidence on comparative safety**

The European Medicines Agency's (EMA) 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 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.

## **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 EMEA guidance notes that, even if an antihypertensive effect has been proven, a significant concern about a detrimental effect on mortality and/or cardiovascular morbidity might lead to a need for outcome studies.

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.

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 who have failed to respond to at least three other agents, who require additional therapy and for whom existing alternatives are ineffective and/or unsuitable. The main clinical trial programme provides no specific data for patients at this stage of treatment. Furthermore, because all trials involved placebo wash-out and run-in periods, none are representative of the proposed niche where aliskiren would be added to the existing therapy of heavily pre-treated patients. Also 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 and secondary care were asked for data on patients who had been prescribed aliskiren for four weeks or more and whose prescribing history indicated that the patient had been treated with three classes of drug.

Expert opinion suggests that the niche proposed for aliskiren at step 4 represents an area of unmet clinical need, however there are concerns about the robustness of the observational data presented for this population and its applicability to clinical practice at this stage of therapy. These are related to:

- How prescribers were selected from within the sample of those prescribing aliskiren and whether such 'early adopters' and their patients are representative of clinical practice.
- Whether methods of BP measurement were as rigorous and consistent as would be expected in controlled trials.

- The definition of a non-responder in these studies, which implies that any SBP reduction would be treated as a response – much less rigorous than the targets for BP response and control identified in controlled trials.
- The fact that patients could be included if they had received three classes of antihypertensive in the past and may not have been receiving these at the time of initiation of aliskiren: only about half of the patients who had been prescribed aliskiren fell into the above category and were included in the analyses.

## 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 on cardiovascular events. Arms were differentiated by the effect of aliskiren and placebo on patients' systolic blood pressure. Other treatments were not considered since the position sought by the manufacturer was when step 4 treatments had failed or were contraindicated and therefore other treatment options were unavailable.

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 UK Prospective Diabetes Study (UKPDS) risk equations, with an annual incidence of diabetes estimate being drawn from NICE guidance.

The effects of aliskiren and placebo on systolic blood pressure for the base case were taken from an eight-week trial from among the placebo-controlled trials of aliskiren monotherapy. Additional treatment effects for aliskiren were drawn from uncontrolled data sourced from a survey of patients at step 4 with a number of GP practices, this yielding a further two values for aliskiren: 4 weeks after initiating aliskiren therapy and last observed value.

The base case estimate was that aliskiren would cost an additional £3,740 per patient and provide an additional 0.145 QALYs, to yield a cost effectiveness estimate of £25,855 per QALY. A sensitivity analysis using baseline characteristics from an observational step 4 cohort yielded a cost effectiveness estimate of £20,725 per QALY, based on a QALY gain of 0.165 and an additional cost of £3,400. Applying the treatment effect from the uncontrolled 4-week GP data resulted in a cost effectiveness of £13,873 (an additional cost of £3,300 and a QALY gain of 0.239) while using the last observation further improved this to £10,104 per QALY (an additional cost of £3,200 and a QALY gain of 0.317).

Base case results were sensitive to the effect on systolic blood pressure: if this fell by less than 12 mmHg the cost effectiveness ratio rose to more than £30,000 per QALY. Results were also sensitive to the inclusion of the diabetic population, which had been relatively crudely modelled compared to other models of diabetes: if this was excluded the cost effectiveness ratio rose to £26,704 per QALY. The manufacturer also assumed zero prevalence of cardiovascular events at baseline: changing this to an arbitrary prevalence of 20% increased the cost effectiveness ratio to £27,231 per QALY.

Weaknesses of the analysis related primarily to the clinical evidence:

- the trial data related to step 1 when the position sought was step 4;
- the step 1 placebo-controlled trial selected was the most optimistic in terms of efficacy;
- the naturalistic data were uncontrolled;
- the manufacturer assumed no co-morbidities (heart failure, previous coronary heart disease, or stroke) at baseline which biased the results slightly in favour of aliskiren;

- the modelling assumed a flat term structure for systolic blood pressure, with aliskiren maintaining its absolute advantage over placebo through time.

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: previous SMC advice

In the absence of a submission from the holder of the marketing authorization SMC issued advice in May 2008: aliskiren (Rasilez<sup>®</sup>) is not recommended for use within NHS Scotland for the treatment of essential hypertension. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.

Following an abbreviated submission, SMC issued advice in October 2006: lercanidipine 20 mg tablet (Zanidip<sup>®</sup>) is accepted for use in NHS Scotland for the treatment of mild to moderate essential hypertension in patients for whom this is an appropriate antihypertensive agent. This new strength allows a reduction in the number of tablets administered at the maximum dose, at reduced cost compared with the formulation available previously.

Following an abbreviated submission, SMC issued advice in August 2006: losartan 100 mg/hydrochlorothiazide 25 mg tablet (Cozaar-Comp 100/25<sup>®</sup>) is accepted for use within NHS Scotland for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy. No increased costs are associated with this product compared with losartan (Cozaar<sup>®</sup>) 100 mg alone. Compared with a previously available combination product it reduces the tablet burden when higher doses of losartan and hydrochlorothiazide are required. This fixed dose combination is one of many options for the treatment of hypertension, including other less expensive angiotensin receptor blocker/diuretic combinations.

Following an abbreviated submission, SMC issued advice in May 2006: olmesartan/hydrochlorothiazide (Olmotec Plus<sup>®</sup>) tablet is accepted for restricted use in NHS Scotland for the treatment of hypertension as an alternative in patients unable to tolerate an ACE inhibitor, whose blood pressure is not adequately controlled by olmesartan 20 mg monotherapy and for whom the addition of a thiazide diuretic is an appropriate next step. There is no additional cost compared to administration of olmesartan alone. The combination

is competitively priced compared with other combinations of angiotensin II antagonists and thiazide diuretics. Angiotensin II receptor antagonists are an alternative to angiotensin converting enzyme (ACE) inhibitors where the latter are not tolerated. This fixed dose combination is one of a number of options for the treatment of hypertension, many of which are less expensive.

Following a full submission, SMC issued advice in September 2004: valsartan /hydrochlorothiazide (Co-Diovan<sup>®</sup>) is accepted for use within NHS Scotland for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on valsartan monotherapy. No increased costs are associated with this product compared with valsartan (Diovan<sup>®</sup>) alone. Angiotensin receptor blockers are an alternative to ACE inhibitors where these are not tolerated. This fixed dose combination is one of many options for the treatment of hypertension, including other angiotensin receptor blocker/diuretic combinations, many of which are less expensive.

Following a full submission, SMC issued advice in November 2003: olmesartan medoxomil (Olmetec<sup>®</sup>) is accepted for restricted use within NHS Scotland. Olmesartan has been shown to be at least as effective as other angiotensin II receptor antagonists (AIIAs) for the treatment of hypertension. It may be considered for use, along with other AIIAs, as an alternative in patients unable to tolerate an ACE inhibitor.”

Following a full submission, SMC issued advice in September 2003: perindopril/indapamide (Coversyl Plus<sup>®</sup>) is recommended for general use within NHS Scotland. Perindopril/indapamide (Coversyl Plus<sup>®</sup>) produces a modest reduction in blood pressure in patients with essential hypertension uncontrolled by perindopril alone. A daily dose of one tablet is almost cost-neutral compared with individual drug preparations.

Following a full submission, SMC issued advice in May 2003: telmisartan /hydrochlorothiazide (MicardisPlus<sup>®</sup>) is recommended for restricted use within NHS Scotland. Telmisartan/hydrochlorothiazide (MicardisPlus<sup>®</sup>) has efficacy similar to the antihypertensive effects of the individual constituents added together in the treatment of essential hypertension. No increased costs are associated with this product compared with telmisartan (Micardis<sup>®</sup>) alone. Angiotensin II receptor antagonists are an alternative to ACE inhibitors where these are not tolerated.

Following an abbreviated submission, SMC issued advice in March 2007: amlodipine /valsartan (Exforge<sup>®</sup>) is accepted for use in NHS Scotland for patients whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy. In patients for whom concomitant use of these medicines as a fixed dose combination is appropriate it allows administration of a single tablet at no greater cost than valsartan (Diovan<sup>®</sup>) alone. Angiotensin receptor blockers are an alternative to ACE inhibitors where these are not tolerated. This fixed dose combination is one of many options for the treatment of hypertension, many of which are less expensive.

Following an abbreviated submission, SMC issued advice in February 2008: valsartan 320 mg tablet (Diovan<sup>®</sup>) is accepted for use in NHS Scotland for the treatment of hypertension. In patients for whom the use of valsartan is appropriate it allows administration of a 320 mg dose as a single tablet at less cost than 2 x 160 mg capsules. Angiotensin receptor blockers are an alternative to ACE inhibitors where these are not tolerated.

Following an abbreviated submission SMC issued advice in June 2008: perindopril arginine (Coversyl Arginine<sup>®</sup>) 2.5mg, 5mg, 10mg tablets are accepted for use in NHS Scotland for the treatment of essential hypertension. The 2.5mg and 5mg tablets are also accepted for treatment of symptomatic heart failure. This advice relates to patients for whom perindopril is

an appropriate choice of therapy. These preparations are also licensed for the reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation, however this indication has not been reviewed by SMC. The arginine salt replaces a tert-butylamine salt previously available and the 2.5mg, 5mg and 10mg arginine tablets are equivalent to the 2mg, 4mg and 8mg tert-butylamine tablets in terms of the content of perindopril base. Caution is therefore required when prescribing perindopril as the two salts are not dose equivalent. Generic preparations of the tert-butylamine salt are available at a lower cost than the proprietary preparations of perindopril.

Following an abbreviated submission SMC issued advice in June 2008: perindopril arginine 5mg/indapamide 1.25mg tablet (Coversyl Arginine Plus<sup>®</sup>) is accepted for use in NHS Scotland for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on perindopril alone and for whom this combination is an appropriate choice of therapy. The 5mg perindopril arginine in this formulation is equivalent in terms of the content of perindopril base to the 4mg perindopril tert-butylamine contained in the formulation previously available. After review of a full submission, SMC issued advice in September 2003 that the previously available formulation of perindopril, indapamide (Coversyl Plus<sup>®</sup>) is recommended for general use within NHS Scotland. It produces a modest reduction in blood pressure in patients with essential hypertension uncontrolled by perindopril alone.

Following an abbreviated submission SMC issued advice in February 2008: losartan 100mg /hydrochlorothiazide 12.5mg tablet (Cozaar-Comp 100/12.5<sup>®</sup>) is accepted for use within NHS Scotland for the treatment of hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy. In patients for whom this combination of antihypertensive agents is appropriate, it allows more flexible dosing than previously available combination products. This fixed dose combination is one of many options for the treatment of hypertension, including other less expensive angiotensin receptor blocker/diuretic combinations.

### **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, who require additional therapy and for whom existing alternatives are ineffective and/or unsuitable. In this scenario the alternative option is to continue with previous treatment, therefore there are no relevant comparators within this niche.

### **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, who require additional therapy and for whom existing alternatives are ineffective and/or unsuitable. In this scenario the alternative option is to continue with previous treatment unchanged, however the costs for a number of other step 4 options are given below for information. 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 range of costs within that class.

<b>Drug</b>	<b>Dose regimen (all oral)</b>	<b>Cost per year (£)</b>
<b>Aliskiren</b>	<b>150mg to 300mg daily</b>	<b>257 to 309</b>
<i>Potassium-sparing diuretics</i>		
Amiloride	5mg to 10mg daily	4.81 to 9.62
Spironolactone	100mg to 400mg daily	68 to 273

<i>Alpha adrenergic blocking drugs</i>		
Doxazosin	2mg to 4mg daily	7.80 to 20
Indoramin	25mg to 100mg twice daily	78 to 312
<i>Beta adrenergic blocking drugs</i>		
Atenolol	5mg to 10mg daily	3.51 to 4.03
Acebutolol	400mg once or twice daily	244 to 488

<i>Loop diuretics</i>		
Furosemide	40mg to 80mg daily	3.25 to 6.50
Bumetanide	1mg daily	15

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 9<sup>th</sup> October 2008.

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 range of costs within that class.

<b>Drug</b>	<b>Dose regimen (all oral)</b>	<b>Cost per year (£)</b>
<b>Aliskiren</b>	<b>150mg to 300mg daily</b>	<b>257 to 309</b>
<i>Angiotensin-converting enzyme inhibitors</i>		
Enalapril	20mg daily	11
Ramipril	2.5mg to 5mg daily	11 to 14
Moexepiril	15mg to 30mg daily	113 to 226

<i>Angiotensin II receptor antagonists</i>		
Candesartan	8mg daily	129
Telmisartan	20mg to 80mg daily	120 to 184
Irbesartan	150mg to 300mg daily	163 to 220

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 9<sup>th</sup> October 2008.

### **Additional information: budget impact**

The manufacturer estimated that around 33,700 patients would remain uncontrolled while on triple therapy, with an additional 12,300 remaining uncontrolled on quadruple therapy in the first year. For those uncontrolled on triple therapy, a market share of 1% (353 patients) in the first year was assumed, rising to 6% (2,557 patients) by year 5. For those uncontrolled on quadruple therapy a market share of 4.8% (621 patients) in the first year was assumed, rising to 10.4% (1,622 patients) by year 5.

This yielded a gross drug cost of £264k in year 1, rising to £1.1m by year 5. Due to the position sought there would be no net drug cost offsets.

**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 14 November 2008.*

*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 reference shaded grey is additional to those supplied with the submission.*

ICH Steering Committee. Principles for clinical evaluation of new antihypertensive drugs. <http://www.emea.europa.eu/pdfs/human/ich/054100en.pdf> 2000

Oh BH, Mitchell J, Herron Jret al. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and sustained 24-hour blood pressure control in patients with hypertension. J Am Coll Cardiol 2007;49:1157-63.

European Medicines Agency (EMA) European Public Assessment Report (EPAR) for aliskiren (Rasilez®), EMA/H/C/780/II/26. [www.emea.europa.eu](http://www.emea.europa.eu)