PUBLIC SUMMARY DOCUMENT
Product: ALISKIREN, tablets, 150 mg and 300 mg (as hemifumarate), Rasilez®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application
To request an Unrestricted Benefit listing intended for the treatment of hypertension.

2. Background
This drug had not previously been considered by the PBAC.

3. Registration Status
Aliskiren was TGA registered on 3 June 2008 for the treatment of hypertension.

4. Listing Requested and PBAC's View
Unrestricted benefit

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
In a patient treated for hypertension where an agent acting on the renin-angiotensin system (RAS) is considered to be clinically indicated by the prescriber, the drugs currently prescribed would be either an angiotensin II receptor antagonist (AIIRA) or an angiotensin converting enzyme (ACE) inhibitor.

Aliskiren is a direct renin inhibitor acting on the RAS and would be an alternative to the AIIRAs and ACE inhibitors which are currently listed on the PBS for the treatment of hypertension.

6. Comparator
The submission nominated irbesartan as the main comparator.

Valsartan, ramipril and lisinopril were nominated as secondary comparators.

The PBAC did not consider this was appropriate, *see Recommendation and Reasons.*

7. Clinical Trials
The submission presented thirteen randomised trials in patients with hypertension comparing aliskiren 150 mg or 300 mg daily with irbesartan 150 mg or 300 mg daily (3 trials), with valsartan 160 mg or 320 mg daily (3 trials), ramipril 5 mg or 10 mg daily (6 trials, including one of the irbesartan trials), and lisinopril 10 mg or 20 mg daily (2 trials). One trial (2303) was in severe hypertension, two trials (2324 and 2344) were in systolic hypertension in the elderly (age ≥65), and one trial (2307) was in diabetes.

The key trials published at the time of submission are shown in the table below:

Trial ID/First author	Protocol title / Publication title	Publication citation
Direct randomised trials: aliskiren versus irbesartan		

Trial ID/First author	Protocol title / Publication title	Publication citation
Trial 2201	Gradman A et al. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients.	Circulation 2005;111: 1012–1018
Trial 2309	Jordan J et al. Direct renin inhibition with aliskiren in obese patients with arterial hypertension.	Hypertension 2007;49:1047-1055
Trial 2351	Palatini P et al. Maintenance of blood-pressure-lowering effect following a missed dose of aliskiren, irbesartan or ramipril: results of a randomized, double-blind study.	J Hum Hypertens. Published online on 21 May 2009; doi:1038/jhh.2009.38
Direct randomised trials: aliskiren versus valsartan		
Trial 2203	Pool J et al. Aliskiren, an orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan.	Am J Hypertens 2007; 20:11–20
Trial 2327	Oparil S et al. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomized, double-blind trial.	Lancet 2007;370:221–229
Trial 2331	Geiger H et al. Combination therapy with various combinations of aliskiren, valsartan and hydrochlorothiazide in hypertensive patients not adequately responsive to hydrochlorothiazide alone.	J Clin Hypertens 2009; 11:1-9.
Direct randomised trials: aliskiren versus ramipril		
Trial 2306	Andersen K et al. Comparative efficacy and safety of aliskiren, an oral direct rennin inhibitor, and ramipril in hypertension: A 6-month, randomised, double-blind trial.	J Hypertens 2008;26:589–599
Trial 2307	Uresin Y et al. Efficacy and safety of the direct rennin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension.	J Renin Angiotensin Aldosterone Syst 2007; 8:190–198.
Trial 2344	Duprez A et al. Aliskiren for geriatric lowering of systolic hypertension: a randomized controlled trial.	J Hum Hypertens 24 December 2009. Advance online publication doi:10.1038//jhh.2009.107
Direct randomised trials: aliskiren versus lisinopril		
Trial 2303	Strasser R et al. A comparison of the tolerability of the direct renin inhibitor aliskiren and lisinopril in patients with severe hypertension.	J Hum Hypertens 2007;21:780-787
Trial 2324	Verdechhia P et al. Safety and efficacy of the oral direct renin inhibitor aliskiren in elderly patients with hypertension.	Blood Pressure 2007;16:381 – 391

Trials in populations other than isolated essential hypertension were located by the sponsor but excluded from the submission. Because these trials and ASPIRE (2010) and Ferdinand 2010, both found during the evaluation, were relevant to the submission's requested unrestricted listing, the results of six of these trials were presented in the evaluation. Two of these trials (1301 and 2316-ALLAY) compared aliskiren with losartan, one trial (Ferdinand 2010) compared aliskiren with amlodipine in combination with hydrochlorothiazide (HCTZ), and three trials were in populations other than isolated essential hypertension (2313-ALOFT, a safety study in heart failure; C2201-AVOID, a study of renal protection in patients with hypertension and diabetes; and ASPIRE (2010), a study of myocardial protection in patients with a recent myocardial infarction with left ventricular dysfunction).

The trials published at the time of submission are shown in the table below:

Trial ID/First author	Protocol title / Publication title	Publication citation
Direct randomised trials: aliskiren versus losartan		

Trial ID/First author	Protocol title / Publication title	Publication citation
Trial 2316 - ALLAY	Solomon S et al. Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy.	Circulation 2009; 119:530-537.
Direct randomised trials: aliskiren versus amlodipine in combination with HCTZ		
Ferdinand et al 2010	Responses to aliskiren/hctz versus amlodipine on peripheral and central blood pressure in African American patients with stage 2 hypertension	J Am Coll Cardiol 55 (10A): A61.E586.
Trials in other populations		
C2201 - AVOID	Parving H et al. Aliskiren combined with losartan in type 2 diabetes and nephropathy.	N Engl J Med 2008; 358:2433-2446.
2313 - ALOFT	McMurray J et al. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure.	Circ Heart Fail 2008; 1:17-24.
ASPIRE 2010	Effect of the direct rennin inhibitor aliskiren on LV remodelling following MI with LV dysfunction.	American College of Cardiology website: http://www.cardiosource.com/rapidnewssummaries/acc10.asp

8. Results of Trials

The results of change from baseline in sitting diastolic blood pressure (DBP) are presented below:

Comparison with irbesartan: There were no statistically significant differences in reduction in DBP between aliskiren 150 mg and irbesartan 150 mg monotherapy, aliskiren 300 mg and irbesartan 300 mg monotherapy, or the same drugs combined with hydrochlorothiazide. Aliskiren 300 mg produced statistically significantly larger reductions in DBP than irbesartan 150 mg (Trial 2201).

Comparison with valsartan: There were statistically significant differences in favour of valsartan for the comparison of aliskiren 150 mg and valsartan 160 mg in Trial 2327 and for both valsartan 160 mg and 320 mg combination treatments with HCTZ in Trial 2331. The submission argued that as the lower bound of the 95% confidence limits for these comparisons was less than 2 mmHg, there are no clinically important differences between aliskiren and valsartan.

Comparison with ramipril: There were no statistically significant differences between monotherapy with aliskiren 150 mg and ramipril 5 mg, and aliskiren 300 mg and ramipril 10 mg in reducing DBP. Aliskiren 300 mg was more effective than ramipril 5 mg (Trial 2339). Aliskiren in combination with HCTZ was statistically significantly more effective than ramipril in combination with HCTZ.

Comparison with lisinopril: There were no statistically significant differences between aliskiren 150 mg or 300 mg and lisinopril 10 mg.

Comparisons with losartan and amlodipine: There were no statistically significant or clinically important differences between aliskiren and losartan or amlodipine.

Overall, the DBP reductions reported in the trials for aliskiren were similar to those reported with the comparator drugs. Where the margin of < 2 mmHg difference in blood pressure

changes was applied, there were no clinically important differences in blood pressure reduction between aliskiren and comparator drugs.

The results of change from baseline in sitting systolic blood pressure (SBP) are presented below:
Comparison with irbesartan: There were no statistically significant differences in reduction in SBP between aliskiren 150 mg and irbesartan 150 mg monotherapy, aliskiren 300 mg and irbesartan 300 mg monotherapy, or the same drugs combined with hydrochlorothiazide.

Comparison with valsartan: There were no statistically significant differences in reduction in SBP between aliskiren 150 mg and valsartan 160 mg monotherapy and aliskiren 300 mg and valsartan 320 mg monotherapy (Trials 2203, 2327). When combined with HCTZ, there was a statistically significant difference in favour of valsartan for the comparison of aliskiren 300 mg and valsartan 320 mg, but not for the aliskiren 150 mg versus valsartan 160 mg comparison (Trial 2331).

Comparison with ramipril: There were statistically significant differences favouring aliskiren between aliskiren 300 mg and ramipril 10 mg in monotherapy (Trials 2307 and 2351) and in combination with HCTZ (Trial 2306). There was no statistically significant difference between monotherapy with aliskiren 150 mg and ramipril 5 mg (Trials 2339 and 2307). Aliskiren 300 mg was more effective than ramipril 5 mg (Trial 2339).

Comparison with lisinopril: There were no statistically significant differences between aliskiren 150 mg or 300 mg and lisinopril 10 mg.

Comparisons with losartan and amlodipine: There were no statistically significant or clinically important differences between aliskiren and losartan or amlodipine.

Overall, neither aliskiren nor the comparator drugs were consistently found to be superior by demonstration of statistically significant differences in blood pressure reduction. Aliskiren was generally similar to comparator drugs regarding blood pressure reduction.

Effectiveness in populations other than isolated hypertension
Trial C2201-AVOID, conducted in hypertensive patients with type 2 diabetes, found that aliskiren plus losartan resulted in greater renal protection compared to the use of losartan alone in urinary albumin to creatinine ratio but not in change from baseline in estimated glomerular filtration rate (GFR).

Trial 2316-ALLAY, conducted in obese patients with hypertension and left ventricular hypertrophy, found aliskiren plus losartan provided no further myocardial protection (as measured by left ventricular mass) beyond that associated with losartan alone. Aliskiren was non-inferior to losartan alone.

The ASPIRE trial demonstrated that aliskiren adds no myocardial protection, as measured by left ventricular end-systolic volume, in a population with reduced left ventricular (LV) function in the context of a recent myocardial infarction (MI). For the secondary outcome, a composite of cardiovascular deaths, heart failure hospitalisations, myocardial infarction, stroke, and resuscitated sudden death, there were 39 (9%) events in aliskiren compared with 34 (9%) in placebo (HR=1.01, 95% CI 0.62, 1.63), and for all-cause mortality there were 17

(4%) deaths in aliskiren compared with 8 (2%) in placebo (HR=1.83, 95% CI 0.79, 4.3). While the results were not statistically significant, these results suggest the possibility of worse outcomes in aliskiren treatment patients. No other cardiovascular morbidity or mortality data were provided in the submission.

A fourth trial, ALOFT, was primarily a safety study in patients with stable heart failure.

None of these trials were designed to address clinical events and there is currently no marker that reliably predicts benefit in cardiovascular morbidity and mortality in heart failure or post-MI with left ventricular dysfunction (Arend 2002). Nonetheless, the finding of more deaths on aliskiren in ASPIRE may suggest the possibility of worse outcomes in aliskiren treatment patients. The submission noted three ongoing randomised outcome trials, ALTITUDE in 8,600 patients with type 2 diabetics at high renal and cardiovascular risk, ATMOSPHERE in 7,000 patients with patients with heart failure and elevated BNP, and ASTRONAUT in 1,800 hospitalised heart failure patients.

For PBAC's view, see Recommendation and Reasons.

Comparative toxicity

Cough: The submission presented a meta-analyses of the incidence of cough comparing aliskiren and AIIRAs (4 trials from the submission) and comparing aliskiren and ACEIs (8 trials from the submission). There was no difference in the aliskiren/AIIRA comparison (17/1302 vs. 10/947, risk difference = 0.00, 95% CI -0.01, 0.02, p=0.88). Aliskiren patients showed less cough in the aliskiren/ACEI comparison (64/3126 vs. 176/2230, risk difference = -0.04, 95% CI -0.06, -0.03, p<0.0001).

Diarrhoea: Although only one trial (Trial 2351) individually showed a more than 2-fold increase in diarrhoea with aliskiren compared to irbesartan, 1.4% versus 0.5%, the TGA evaluation indicated diarrhoea rates of 1.2%, 1.3%, 1.2%, 2.3%, and 9.5% for placebo, 75 mg, 150 mg, 300 mg, and 600 mg aliskiren, respectively.

Peripheral oedema: Although an excess of peripheral oedema adverse events was not seen in the clinical trials, cases reported since marketing often showed a positive rechallenge increasing the likelihood of causation.

Aliskiren is associated with an increased risk of diarrhoea and appears to be associated with an increased risk of peripheral oedema. It also has a risk of hyperkalemia in certain settings, although the analysis presented was unable to detect a difference in this risk compared to the risk of hyperkalemia with ACEIs or AIIRAs. There are limited comparative data (four short-term trials) on the co-use of aliskiren with either an ACEI or an AIIRA. There are few long-term comparative safety data of aliskiren with only three of the trials having a duration of more than 6 months and none beyond one year.

Risks identified by the TGA, to be included in the regulatory Risk Management Plan for aliskiren, include diarrhoea, rash, angioedema and anaphylaxis, hyperkalemia, decreased haemoglobin and hematocrit, and renal dysfunction. Potential risks in the Risk Management Plan are colorectal hyperplasia, peripheral oedema, and hypotension.

9. Clinical Claim

The submission described aliskiren as similar in terms of comparative effectiveness and similar in terms of comparative safety over irbesartan.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as aliskiren 150 mg daily and irbesartan 150 mg daily and valsartan 160 mg daily, plus aliskiren 300 mg daily and irbesartan 300 mg daily and valsartan 320 mg daily.

11. Estimated PBS Usage and Financial Implications

The financial savings/year to the PBS was estimated by the submission to be less than $10 million per year in Year 5. The estimate is based on the assumption that aliskiren replaces AIIRA use only. A sensitivity analysis assuming 35.5% of substitution is from ACEI results in a cost to the PBS of less than $10 million per year in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC acknowledged that aliskiren was the first drug in a new class of antihypertensives and it lowers blood pressure effectively. Similar reductions in blood pressure were seen compared with irbesartan, other AIIRAs and ACEIs. However, the PBAC noted that unlike the ACE inhibitors and AIIRAs, no reduction in cardiovascular mortality and morbidity has been demonstrated, and there are currently no additional indications such as use in heart failure, post MI, vascular disease and renal disease.

Therefore, the Committee considered, on the evidence presented in the submission, that aliskiren was similar in efficacy to irbesartan in blood pressure reduction only. The PBAC also considered that the claim of similar comparative safety to irbesartan may not be reasonable as there are no long-term safety data and a number of safety issues to be addressed by Risk Management Plans.

The PBAC did not agree that the comparator should be restricted to irbesartan as the main comparator, and valsartan, ramipril and lisinopril as secondary comparators. The PBAC considered that the comparator should include a mix of all PBS-subsidised antihypertensive agents including AIIRAs, ACEIs, calcium channel blockers, beta-blockers and thiazide diuretics. The PBAC agreed with the ESC that the relative market share of AIIRAs and ACEIs did not inform the choice of comparator adequately, particularly as aliskiren may be used in combination with conventional therapy, rather than as a substitute and that clinicians were unlikely to replace current antihypertensive therapies with a newer agent without long term outcome and safety data.

The PBAC noted that the base case estimates of extent of use and financial implications were based on the assumption that aliskiren would replace AIIRAs only. The PBAC considered that in clinical practice it was more likely that a proportion of substitution would be from ACEIs, calcium channel blockers and other antihypertensive agents and also from use as an add-on therapy rather than as a direct substitute. Therefore the uptake rates are likely underestimated as they are lower than for recently listed AIIRAs and it is likely that uptake of a drug in a new class will be greater than for another AIIRA.

The PBAC therefore rejected the submission for aliskiren on the basis of uncertain clinical need for an anti-hypertensive as it does not provide evidence of long-term clinical benefits compared with other agents in similar therapeutic classes and uncertain cost effectiveness.

The PBAC noted that the submission meets the criteria for an independent review.

Recommendation:
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has no further comment.