All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report:

Aliskiren (Rasilez®▼) for the treatment of essential hypertension

Novartis Pharma UK Ltd

Advice No: 0409 – June 2009

Recommendation of AWMSG

Aliskiren (Rasilez®▼) is not recommended for use within NHS Wales for the treatment of essential hypertension. The clinical and cost effectiveness data presented was insufficient for AWMSG to recommend its use.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 24th June 2009

The recommendation of AWMSG is:

Aliskiren (Rasilez®▼) is not recommended for use within NHS Wales for the treatment of essential hypertension. The clinical and cost effectiveness data presented was insufficient for AWMSG to recommend its use.

Additional note:

- There are no clinical trials comparing aliskiren (Rasilez®▼) with other antihypertensive treatments recommended at step 4 of the NICE guidelines, which was the context of the submission.

ABBREVIATIONS

ACEI	Angiotensin converting enzyme inhibitor
ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
Ang II	Angiotensin II
ARB	Angiotensin II receptor blocker
AWMSG	All Wales Medicines Strategy Group
BHS	British Hypertension Society
BMI	Body mass index
BP	Blood pressure
CCB	Calcium channel blocker
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CV	Cardiovascular
CVD	Cardiovascular disease
CYP450	Cytochrome P450
EMEA	European medicines agency
EPAR	European Public Assessment Report
HbA1c	Glycosylated haemoglobin
HCTZ	Hydrochlorothiazide
HDL	High-density lipoprotein
ITT	Intention-to-treat
LSM	Least squares mean
MI	Myocardial infarction
mDBP	Mean diastolic blood pressure
mSBP	Mean systolic blood pressure
msDBP	Mean sitting diastolic blood pressure
msSBP	Mean sitting systolic blood pressure
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMG	New Medicines Group
NPC	National Prescribing Centre
OD	Once daily
P-gp	P-glycoprotein
PRA	Plasma renin activity
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RAS	Renin angiotensin system
RC	Renin concentration
RCT	Randomised controlled trial
SAE	Serious adverse event
SPC	Summary of Product Characteristics
UKPDS	United Kingdom Prospective Diabetes Study
WMP	Welsh Medicines Partnership

2.0 PRODUCT DETAILS

2.1 Licensed indication
Aliskiren (Rasilez®▼) is indicated for the treatment of essential hypertension[1].

The company submission proposes that aliskiren should be considered for restricted use; as an alternative option for add-on therapy at step 4 of the National Institute for Health and Clinical Excellence (NICE) treatment guidelines[2].

2.2 Dosing
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[1].

Aliskiren is not recommended for use in children and adolescents below the age of 18 and caution should be exercised in hypertensive patients with severe renal impairment due to a lack of data on safety and efficacy[1].

See the Summary of Product Characteristics (SPC) for full details[1].

2.3 Market authorisation date
22nd August 2007[2].

2.4 UK Launch date
3rd September 2007[3].

3.0 DECISION CONTEXT

Essential hypertension is a major risk factor for cardiovascular disease (CVD); stroke, myocardial infarction (MI) and congestive heart failure (CHF). It is widely recognised that adequate control of essential hypertension is important to significantly decrease mortality and morbidity[4]. In Wales, the prevalence of hypertension is estimated at 14.26%[5] with 378,000 patients currently being treated for essential hypertension[6]. Approximately 24% of these patients (91,000) remain uncontrolled, of which 20,191 and 6985 are on triple and quadruple therapy, respectively[2].

The British Hypertension Society (BHS) classification for hypertension is outlined in Appendix 1[7]. Current National Institute for Health and Clinical Excellence (NICE) and BHS guidelines for the management of essential hypertension recommend treatment in a stepwise manner for newly diagnosed patients[8]. Treatment recommendations include an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) (A), a calcium-channel blocker (CCB) (C) and a diuretic (D) (this treatment regimen will be referred to as the A/C/D algorithm; steps 1-3. Treatment choice will depend on the individual patient, with the usual aim of maintaining BP at ≤140/90mmHg[8]. A lower BP target (≤130/80mmHg) is recommended in high-risk patient populations such as those with target organ damage, diabetes mellitus or renal disease[8]. Treatment with a fourth drug (step 4) is suggested if a patient's BP is uncontrolled despite therapy with steps 1-3[8]. Currently, step 4 treatment options include:

(i) Further diuretic therapy
(ii) Alpha-blocker
(iii) Beta-blocker

Treatment of uncontrolled hypertensive patients at step 4 can often prove challenging and clinicians are faced with choosing one of the existing recommended therapies, with little clinical evidence regarding their use at step 4[2, 8].

Aliskiren is the first in a new class of renin angiotensin system (RAS) antihypertensive drugs licensed for the treatment of essential hypertension[2]. Aliskiren is a selective and direct renin inhibitor and therefore inhibits the production of angiotensin II (Ang II) by blocking the RAS at its point of activation. Since angiotensinogen is the only known physiological substrate of renin, specific inhibition of the RAS by diminishing renin activity has the advantage of not interfering with other metabolic pathways[4].

Aliskiren is licensed for the treatment of essential hypertension, although the company submission proposes that aliskiren should be considered for restricted use in Wales; as an alternative option for add-on therapy at step 4 of the NICE treatment guidelines[2].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The company submission is based on one randomised, double-blind, placebo controlled, Phase III trial (study 2308) and a naturalistic survey consisting of observational data collected from primary and secondary care clinicians experienced in the use of aliskiren. Study 2308 compared aliskiren 150mg and 300mg daily with placebo in patients with mild to moderate essential hypertension. After eight weeks there was a clinically and statistically significant decrease from baseline in the mean sitting diastolic blood pressure (msDBP) for both doses of aliskiren when compared to placebo. The naturalistic review demonstrated a beneficial role for aliskiren in reducing BP in patients uncontrolled despite following steps 1 to 3 of the NICE guideline treatment options. This review showed that aliskiren treatment at this stage provided clinically important reductions in mean systolic BP (mSBP) after four weeks, with similar effects reported from both primary and secondary care. A number of other studies referenced in the company submission showed that aliskiren monotherapy was superior to placebo at reducing BP. The company however only used study 2308 in their submission as some of these other trials utilised an earlier capsule formulation which could not definitively support efficacy for the marketed tablet formulation. Aliskiren combination therapy did not demonstrate significant differences in BP reduction when compared to alternative combination treatment.

There are no studies comparing aliskiren with other currently recommended step 4 antihypertensive treatment options and study 2308 only provides evidence of efficacy at step 1 versus placebo. Although change in BP is accepted as a surrogate endpoint in studies for antihypertensive agents, none of the aliskiren studies were designed to analyse mortality or morbidity data or assess target organ damage. The European Medicines Agency (EMEA) guidance notes that even if an antihypertensive effect has been proven, the beneficial effects of aliskiren on mortality and cardiovascular morbidity and target organ damage are unknown, therefore there is a clear need for further outcome studies.

In the studies considered within the company submission the overall number of treatment related adverse events (AEs) were minimal. There were no significant differences between treatment groups and those reported were considered mild, although it is important to bear in mind the short duration of all trials.

4.2 Review of the evidence on cost- effectiveness

The company submission describes three cost utility analyses of aliskiren compared with placebo. The base case analysis relates to first-line use of aliskiren and is based on the study population and antihypertensive efficacy observed in study 2308. The additional analyses relate to a simulated patient population of patients who have failed treatment with three classes of antihypertensive (i.e. patients at step 4 of the NICE treatment algorithm) and the company proposes that aliskiren is restricted for use in these patients. In the first of these additional analyses, antihypertensive efficacy is based on study 2308, and the second is based on data obtained from a UK survey conducted in primary care.

In the base case analysis, in patients using aliskiren as a first-line treatment, the incremental cost per quality adjusted life year (QALY) gained for aliskiren compared with placebo is estimated to be £25,855. In the treatment of patients at step 4 of the NICE treatment algorithm, the incremental cost per QALY gained compared with placebo is estimated to be £20,725 when efficacy is based on that in study 2308, and £13,873 when based on four-week uncontrolled, observational data from the GP survey.

It should be noted that placebo would not be an appropriate comparator in any of these analyses, given the range of antihypertensive agents that are available. These analyses are therefore unlikely to reflect the true cost-effectiveness of aliskiren when used in clinical practice. As aliskiren has not been demonstrated to improve cardiovascular (CV) outcomes for patients with any degree of hypertension, CV outcomes have been modelled using SBP effects as one of several inputs into CV risk equations. There are some potential issues with the selective use of efficacy data from study 2308 and the use of uncontrolled, observational data from the survey of GPs. Sensitivity analyses indicate that the model is sensitive to the assumed reduction in SBP achieved with aliskiren, which is important given the potential issues with the sources of antihypertensive efficacy data that have been used.

5.0 LIMITATIONS OF DECISION CONTEXT

- Study 2308 only provides evidence of efficacy at step 1 versus placebo whereas the company submission proposes aliskiren treatment as a step 4 option of the NICE guidelines
- There are no clinical trials comparing aliskiren with other antihypertensive treatments at step 4 of the NICE guidelines
- The patient population from the Phase III trial is not representative of the target population for aliskiren treatment in clinical practice, as trial patients either had a washout period of medication prior to the study or were new patients not previously treated in accordance with steps 1 to 3 of the NICE guidelines
- All the studies were carried out in mild to moderate essential hypertensive patients, whereas patients at step 4 may be more likely to have severe, treatment resistant hypertension which is not totally reflective of the patient populations studied
- The only evidence of clinical efficacy for aliskiren at step 4 of the NICE guideline is from the naturalistic study which uses uncontrolled, observational data from review of a small survey of primary care (n=223) and secondary care (n=37) prescribing
- The main trial included in the submission was of short duration (eight weeks), limiting the available evidence for potential improvement of long-term CV outcomes or safety in patients with hypertension

- The economic evidence presented in support of aliskiren is limited by the inappropriate use of placebo as a comparator in all of the analyses that have been presented in the company submission. The analyses that are presented are therefore unlikely to reflect the true cost effectiveness of aliskiren in clinical practice

6.0 CLINICAL EVIDENCE

The company submission is based on study 2308, a Phase III trial (which compared aliskiren to placebo)[9] and a naturalistic survey which included two observational studies; one in primary care and the other in secondary care[10, 11]. The company include reference to a number of trials comparing aliskiren therapy to standard ARB, ACEI and diuretic therapy, although chose only to use study 2308 in their submission as some of the other trials utilised an earlier capsule formulation which could not definitively support efficacy for the marketed tablet formulation[2]. The primary outcomes from the most relevant supporting studies are briefly summarised in section 6.1.3. Further details of these trials can be found in the company submission (appendix C and D)[2]. The recommended daily dose for patients with essential hypertension is 150mg or 300mg for patients whose BP is not adequately controlled[1], therefore the data from the 600mg treatment group is not discussed in detail in this report.

6.1 Clinical efficacy

6.1.1 Phase III trial of aliskiren compared with placebo – Study 2308[9]

This study was an eight-week phase III multicentre, randomised, double blind, placebo-controlled, parallel group trial that compared aliskiren with placebo as a monotherapy agent for patients with essential hypertension. Adults (≥18 years) with mild to moderate hypertension (msDBP ≥95mmHg and ≤110mmHg) were recruited from 68 international centres. Patients were excluded from the study if they had severe hypertension (msDBP ≥110mm Hg) or secondary hypertension; a history of serious cardiac or cerebrovascular disease; type 1 or 2 diabetes mellitus with poor glycaemic control; or any condition that may affect the absorption, distribution, metabolism of the study drug. Patients (n=672) were randomised to one of the four treatment groups (aliskiren 150, 300, or 600mg or placebo) and double blind treatment was administered once daily for eight weeks. Follow-up visits were conducted every two weeks during the eight-week treatment period. The primary efficacy population was the intent-to-treat (ITT) population, which was comprised of all randomised patients who had baseline and at least one post-baseline efficacy measurement during the double-blind treatment period. Patients completing the eight-week, double blind treatment period entered a two-week, treatment free withdrawal period and follow-up was at four days and two weeks[2, 9].

The primary objective of this study was to evaluate the msDBP lowering effects of aliskiren (150mg, 300mg) compared to placebo in patients with essential hypertension. The secondary objectives were to:

- Evaluate the dose-response relationship of the BP lowering effects across the dosage range
- Assess the reductions in mean sitting systolic BP (msSBP)
- Evaluate the 24-hour ambulatory BP monitoring (ABPM) profiles and trough-to-peak ratios for aliskiren
- Assess the proportion of patients achieving successful treatment response (defined as msDBP ≤90mm Hg and/or ≥10mm Hg reduction from baseline) or BP control (BP≤140/90mm Hg)

- Evaluate the effects of aliskiren treatment and treatment withdrawal on plasma renin activity (PRA) and renin concentration (RC)
- Evaluate the safety and tolerability of aliskiren compared to placebo[9]

Aliskiren (150mg, 300mg) was significantly superior to placebo in lowering msDBP and msSBP in the ITT population. Pairwise comparisons showed a statistically significant reduction in msDBP from baseline with aliskiren 150mg and 300mg compared to placebo (difference in change from baseline was 5.4mmHg and 6.18mmHg respectively; [p<0.0001]). The BP reductions observed in this study were related to the dose of aliskiren, although the dose-response relationship was shallow[9]. Overall, the proportion of patients achieving a successful treatment response was significantly higher with aliskiren (59.3% and 63.3% with 150mg and 300mg, respectively) compared to placebo (36.2%). There was also a significantly higher number of patients with controlled BP in the 150mg and 300mg aliskiren treatment groups (35.9% and 41.6%, respectively) compared to placebo (20.3%)[2, 9]. Appendix 2, Table 1A shows outcome details for study 2308.

BP reduction (approximately 70-80% of maximal reductions) was apparent by week two and a maximal or near maximal reduction was achieved by week four and maintained throughout the eight-week treatment period. BP increased gradually after treatment withdrawal, but did not return to baseline by the end of the two weeks and there was no evidence of rebound effects, which can be a problem with some antihypertensive agents[7]. In a subgroup of 216 patients, ABPM demonstrated that aliskiren-induced BP reductions are maintained throughout the 24 hour dosing period[2, 9].

Points to note:

- Study 2308 only provides evidence of efficacy at step 1 versus placebo whereas the company submission proposes aliskiren treatment as a step 4 option of the NICE guidelines
- Patients either had a washout period of medication prior to the study or were new patients not previously treated in accordance with steps 1 to 3 of the NICE guideline
- The company propose that aliskiren treatment should be aimed at uncontrolled, difficult to treat patients, although no information is given regarding the treatment history of these patients
- The mean age of patients was 53 years; 87% were ≤ 65 years and only 13% were ≥65 years. There was also a higher percentage of male (61.6%) and caucasian (61.3%) patients compared to female and other ethnicities respectively
- Patients with diabetes with poor glycaemic control were excluded from this trial, but in practice may constitute a significant percentage of the population with hypertension resistant to steps 1 to 3 of the NICE guidelines
- Although there was a dose-dependent decrease in msDBP at week 8; this is not proven to be statistically significant as the dose response relationship was shallow
- It is worth reflecting that current NICE guidance recommends antihypertensive drug treatment in patients with persistent high BP of 160/100mmHg or more, or persistent BP above 140/90 mmHg and raised CV risk (10-year risk of CVD of at least 20%, existing CVD or target organ damage). The msBP (SBP/DBP) of all patients in the trial at baseline was reported as 152.1/99.6mmHg[2]. It is therefore possible that a proportion of the patients in this trial would not have been recommended antihypertensive drug treatment based on current guidelines[8]

6.1.2 UK Naturalistic review: Aliskiren use in BHS step 4 hypertensive patients[10, 11]

To support the use of aliskiren at step 4 of the NICE guidelines[8] the company submission includes a naturalistic review combined of two observational studies; one of which surveyed GPs who had prescribed aliskiren while the other surveyed hospital physicians experienced in its use.

The primary aim of this study was to typify the patients in whom aliskiren was being used and to quantify any BP changes that were observed in a naturalistic setting. The data collected from the primary care setting was from patients who had been treated with either 150mg or 300mg of aliskiren for at least four weeks. Patients (n=223) were reported receiving either 150mg (83%) or 300mg (17%). Of the 184 patients prescribed aliskiren 150mg, 90 (49%) had been treated using the A/C/D treatment options. These patients achieved a mean reduction in SBP of 17.25mmHg after 4 weeks treatment. Four of these patients were classified as non-responders (had no change in SBP). Of the 39 patients prescribed aliskiren 300mg, 26 (67%) had been treated using the A/C/D treatment options. These patients achieved a mean reduction in SBP of 15.7mmHg after 4 weeks treatment. Two of these patients were classified as non-responders [2, 10].

A similar naturalistic survey in a secondary care setting supported the findings from the primary care survey, although the number of patients was small (n=37). A mean reduction in SBP of 27mmHg was observed in three hospital patients taking 150mg aliskiren and 11mmHg in 19 patients taking 300mg aliskiren[2, 11].

Points to note:

- It must be noted that the naturalistic survey uses uncontrolled, observational data from a review of a small survey of primary and secondary care prescribing
- The data shows that 52% of patients prescribed aliskiren in primary care, have been treated with all classes of agents recommended at steps 1-3 and still require treatment with a fourth drug. No data has been made available with regard to the treatment history of the remaining 48% of patients
- Clinically meaningful BP reductions are achieved with aliskiren (150mg) in patients who have been difficult to treat with other antihypertensive therapy
- Information is not available on prescriber selection. It would be essential to know if early adoption of new medicines is representative across a wider section of practice
- It must be noted that this is observational data and methods of BP measurement may not be as consistent as would be expected within a controlled trial

6.1.3 Summary of supporting evidence

A number of trials have been published which support the antihypertensive efficacy of aliskiren[12]. Studies have shown that aliskiren monotherapy is effective at reducing BP and is clinically significant when compared to placebo[9, 13-17]. Many studies have compared the effects of aliskiren to other antihypertensive monotherapy and the evidence indicates that the BP lowering effect of aliskiren is similar to that observed with other antihypertensive drugs. Aliskiren treatment was not superior to treatment with a thiazide diuretic (hydrochlorothiazide [HCTZ])[16], ACE inhibitor (ramipril)[18], or an ARB (valsartan[13, 14] and losartan[19]). The data also supports aliskiren combination therapy in being more effective at lowering BP compared to either monotherapy alone[14, 16, 18, 20, 21], but that aliskiren combination therapy was similar in effectiveness to other drug combinations[13, 21]. For more details on these studies see table 3c and appendix C within the company submission[2].

Points to note

- Although aliskiren treatment was superior to placebo at reducing BP, there were no significant differences in the reduction of msDBP when aliskiren was compared to alternative antihypertensive monotherapy
- Likewise no significant differences were observed in the BP lowering effects of aliskiren combination therapy compared to other combination therapy
- The published trials on the use of aliskiren mainly focus on BP lowering in patients with mild to moderate hypertension
- The length of the trials were eight weeks on average and therefore not designed to ascertain effect on mortality, CV morbidity and target organ damage

6.2 Safety

In the study discussed in section 6.1.1 aliskiren was shown to be well tolerated and the rates of reported AEs were similar to placebo[2, 9]. The most frequent reported AEs were headaches and nasopharyngitis, but similar or greater incidence was reported in the placebo group compared to aliskiren (headache: 7.0%, 7.7% and 9.7%, nasopharyngitis: 2.9%, 3.6% and 6.1% in 150mg, 300mg aliskiren and placebo group, respectively)[9]. Overall, there were few discontinuations due to AEs, and the frequency was lower in the active treatment groups (0.6%, 1.8% and 3.6% in 150mg, 300mg aliskiren and placebo group respectively). There were three serious AEs (SAEs) but these were not suspected to be treatment related and no deaths occurred during the study (see appendix D in the Form B submission[2])[9]. These findings were supported in a pooled analysis by Weir and colleagues from five placebo-controlled efficacy/safety trials to investigate the rate and type of AEs with aliskiren monotherapy[22]. The incidence of AEs for each aliskiren dose was similar to placebo (37.5%, 40.2% and 40.2% for aliskiren 150mg, 300mg and placebo, respectively) and few patients discontinued due to AEs (1.6%, 2.6% and 3.5% for aliskiren 150mg, 300mg and placebo, respectively). Overall >95% of AEs were mild or moderate in intensity and the most common were headache, nasopharyngitis, diarrhoea and dizziness. The incidence of SAEs for aliskiren was low (0.4% and 0.5% for 150mg and 300mg, respectively) and similar to that of placebo (0.6%)[2, 22].

The SPC states that patients receiving other medicinal products inhibiting the RAS and/or those with reduced kidney function and/or diabetes mellitus are at an increased risk of hyperkalemia during aliskiren therapy[1]. As with any agent acting on the RAS, routine monitoring of electrolytes and renal function is indicated in patients with diabetes mellitus, kidney disease or heart failure. Although the AE profile for aliskiren was not significantly different to placebo or an active comparator it is important however, to bear in mind the short duration of these randomised controlled trials (RCTs).

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

Aliskiren is licensed for essential hypertension[1] and therefore any anthypertensive drug used (at any step) in the treatment of essential hypertension would be considered a suitable comparator. These include ACEIs (e.g. lisinopril, ramipril); ARBs (e.g. irbesartan, losartan, valsartan), CCB (e.g. amlodipine), or a diuretic (e.g. HCTZ). However, the company submission requests the consideration of aliskiren at step 4 of the NICE guidelines for patients who have failed to respond to at least three other agents and whom require additional therapy. Current recommended alternative antihypertensive therapies used to treat hypertension at this stage, which would therefore be appropriate comparators for determination of the comparative efficacy and safety, include[8]:

- Further diuretic therapy
- Alpha blockers
- Beta blockers

7.2 Comparative effectiveness

- There are a number of trials referred to in the company submission that compare aliskiren with an active comparator (thiazide diuretic (HCTZ), ACEI, ARB, CCB). These studies have shown similar clinical effectiveness between aliskiren monotherapy and an active comparator. Likewise similar efficacy was shown with aliskiren combination therapy and alternative antihypertensive combination therapy[12]
- In line with NICE guidelines, current antihypertensive options at step 4 include diuretics, alpha blockers and beta blockers[8]. None of the trials outlined in the submission compare aliskiren therapy to currently recommended step 4 treatment
- There are safety issues with all current step 4 therapy options which need to be considered when choosing the most appropriate treatment option
- The company submission requests consideration for aliskiren treatment in uncontrolled, difficult to treat patients. However no information is given regarding the treatment history of these patients and in the RCT discussed in section 6.1.1 some patients have received no prior antihypertensive treatment. It is therefore difficult to assess the comparative effectiveness of aliskiren with regard to its suggested place in therapy
- In study 2308, ABPM in patients treated with aliskiren indicated significant 24 hour BP control which is consistent with aliskiren's long half life (34 to 41 hours). Compared to shorter acting products this may minimise the risk of CV events occurring in the morning[9]

8.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issue for AWMSG to consider is whether any additional benefits offered by aliskiren over the relevant comparator(s) justify any additional costs and, if so, whether the total budgetary impact of supporting the use of aliskiren is acceptable.

8.2 Description and critique of the company's submission

The company submission describes a base case cost utility analysis of aliskiren monotherapy compared against placebo, based primarily on the subjects and efficacy data from study 2308 (see section 6). Two further analyses are presented of aliskiren compared with placebo, in which a cohort of patients at step 4 of the NICE hypertension treatment algorithm has been modelled based on patients receiving fourth-line antihypertensives in a Glasgow blood pressure clinic. In the first of these, efficacy data for aliskiren are still based on data from study 2308. In the second of these, survey data on patients taking aliskiren in UK primary and secondary care centres has been used.

A Markov model has been developed in which SBP, alongside other risk factors for the development of CVD, determines the probabilities of moving through the modelled health states. In contrast to several other classes of antihypertensive agents, there are no CV outcomes data available for aliskiren. Therefore, transition probabilities relating to CV events are derived from Framingham CV risk equations and United Kingdom Prospective Diabetes Study (UKPDS) risk equations. These are supplemented with several other sources to predict risks of subsequent CV events and deaths.

Assumptions have been made where data are incomplete for all inputs required for these risk equations.

The base case model has a number of limitations. The use of aliskiren monotherapy would appear to represent first-line treatment of patients at step 1 of the NICE treatment algorithm, and the efficacy data are based on one trial conducted in patients with mild-to-moderate hypertension. This trial is one of the most favourable of the placebo-controlled trials and its use may still be considered selective, although the impact of SBP reductions has been tested in sensitivity analyses. Moreover, a placebo comparator would be wholly inappropriate in these patients, given the range of treatment options that are available.

The company proposes that aliskiren would be best restricted for use in patients at step 4 of the NICE treatment guideline. The two analyses that have been conducted in an attempt to support this proposition also have several limitations. Whilst efforts have been made to simulate an appropriate cohort, in the first of these analyses the efficacy data for aliskiren is still based on that observed in the monotherapy setting, in patients who are unlikely to be representative of the patients being modelled. In the second of these analyses, efficacy data are taken from a retrospective audit of patients receiving aliskiren in primary care settings in the UK. Placebo is also used as the comparator for these two additional analyses, which would seem inappropriate when alternatives such as beta-blockers, alpha-blockers and additional diuretic therapy are recommended as options for patients at step 4 of the NICE treatment algorithm.

As the model has not been provided to the Welsh Medicines Partnership (WMP), the model inputs and outputs have not been verified.

8.3 Population

In the base case analysis, the baseline characteristics of patients who received placebo or aliskiren 150mg daily in study 2308 are used to simulate the patient cohort. These patients were required to have DBP of $\geq$95mmHg and <110mmHg, and those with severe hypertension were excluded. The msBP (SBP/DBP) of all patients in the trial at baseline was reported as 152.1/99.6mmHg[2]. It is worth reflecting that current NICE guidance recommends antihypertensive drug treatment in patients with persistent high BP of 160/100mmHg or more, or persistent BP above 140/90 mmHg and raised CV risk (10-year risk of CVD of at least 20%, existing CVD or target organ damage)[8]. It is possible that a proportion of the patients in this trial would not have been recommended antihypertensive drug treatment based on current guidelines. The fact that this was a placebo-controlled trial, rather than active-controlled, lends some credence to this possibility. In addition, as data were lacking, it has been assumed that no patients in study 2308 are smokers. This would influence the CVD risk estimates, although to the same degree in both the aliskiren and placebo arms. The assumption that evidence of efficacy obtained from this patient group is applicable to patients at step 4 of the NICE treatment algorithm, as is assumed in the first of the additional analyses, would seem subject to some uncertainty.

For the two additional analyses, data from a cohort of patients attending a large blood pressure clinic in Glasgow have been used[2, 23]. This clinic hosts a database, which has been used to provide characteristics of patients who have been prescribed an ACEI /ARB, CCB and diuretic drug, either prior to or at the time of their first clinic contact and in any combination or alone as deemed appropriate by their clinician. The company considers that this patient cohort appropriately represents patients who would be at step 4 of the NICE treatment guideline, and has compared the characteristics with those of a similar cohort contained within the Health Outcomes Data Repository (HODaR) database, which uses secondary care data from Cardiff and Vale NHS

Trust[2]. As the HODaR data do not provide actual BP readings for these patients, the Glasgow clinic data have been used[2]. It should be noted that some important patient characteristics, required as inputs for the CVD risk equations, were also not available from the Glasgow clinic database, and so these parameters (e.g. glycosylated haemoglobin (HbA1c), total and high-density lipoprotein (HDL) -cholesterol) have been assumed from the baseline characteristics of patients in study 2308[2]. In addition, it is assumed that there are no important co-morbidities (e.g. heart failure, previous history of CVD) at baseline. These assumptions would be associated with a degree of uncertainty in the estimated risk of CV events, and some of these parameters have been tested in sensitivity analysis.

8.4 Perspective and time horizon

The analysis was conducted from the perspective of NHS Wales, taking account of direct medical costs. A time horizon of 30 years has been used in the base case analysis. With the average patient age at baseline being 52.5 years[2], this would probably be sufficient to capture the vast majority of relevant outcomes and costs, although a lifetime horizon would be most appropriate. Sensitivity analysis considers time horizons of 10-50 years. A six-month cycle length is used, as was used for the model developed for the NICE clinical guideline[2].

8.5 Comparator

No comparators have been used for the base-case analysis and the two additional analyses, which would seem to be inappropriate for addressing the current decision problem.

In the base case analysis, which in essence represents first-line treatment of hypertension (step 1 in the NICE treatment algorithm), the use of placebo as the comparator is inappropriate. In the majority of patients like those in study 2308 (mean age around 52.5 years, around 15% black race) who require initiation of drug treatment (and it is not clear that all patients in study 2308 would necessarily meet the current recommended criteria from NICE), the preferred first-line treatment would be an ACE inhibitor[8].

In the additional analyses, which are intended to consider patients at step 4 of the NICE treatment algorithm, other potential agents to add into step 3 agents include beta-blockers , alpha-blockers or additional diuretics[8]. It is possible that none of these agents would be appropriate for some of these patients; however, this would be unlikely to be the case for all patients. The justification provided in the company submission for not using a specific comparator in the additional analyses is that there is a lack of efficacy data available in support of any agent at step 4 of the NICE treatment algorithm, which precludes a robust analysis[2]. It should also be considered that this is the case for aliskiren and, given that alternative agents do exist and are recommended as options for use by NICE, an analysis based on no comparator is also unable to provide a robust estimate of the true cost effectiveness of aliskiren when used in patients at step 4 of the NICE treatment algorithm.

8.6 Clinical inputs

8.6.1 Efficacy data

In contrast to many other antihypertensive agents that are available, aliskiren has not been demonstrated to improve CV outcomes in patients with any degree of hypertension. Therefore, the clinical outcomes from aliskiren treatment have been modelled from its antihypertensive efficacy. Age, sex, race, SBP and various other parameters from the modelled patient cohorts are reportedly used as inputs to Framingham heart study CV risk equations[24-26] to determine the risk of a first coronary heart disease (CHD) event. The risk of a first CV event in patients with diabetes is

reportedly based on risk equations from UKPDS data (no reference cited). The risk of subsequent CV events (CHD, stroke, heart failure) are reportedly based on further Framingham risk equations, although the reference cited for subsequent stroke events appears to relate only to CHD events[27]. The risk of development of diabetes is based on the rate assumed in the NICE clinical guideline[8]. The risk of death following a CHD event is based on a reanalysis of the Seven Countries Study[28], which was performed to inform a European CVD risk chart. The risk of death following a stroke is based on that found in a meta-analysis of studies of primary prevention using aspirin[29]. The risk of death due to heart failure has been estimated from Framingham heart study data[30], using a number of transformations of the data to derive heart failure survival curves, and is dependent on time since its onset[2]. Such modelling, based on several sources and assumptions, is likely to involve a degree of uncertainty in relation to the predicted outcomes.

The company submission reports that the model was originally designed to allow treatment switching among antihypertensive treatments and to track patients through a range of hypertensive interventions[2]. However, treatment switching is not permitted in the analyses presented in the company submission, as it is assumed that aliskiren is a final therapeutic option[2]. This appears to be so even in the base case analysis, which represents first-line treatment.

8.6.1.1 Base case analysis

In the base case analysis, the SBP values and other parameter inputs for the CVD risk equations are based on baseline characteristics and 8-week results of study 2308. Assumptions are used where data are lacking, such as the proportion of subjects that are smokers[2]. There have been several other placebo-controlled and active controlled studies of aliskiren, and the reasons included in the company submission for selecting study 2308 to provide the efficacy data include relevance of the study population to the Welsh population, the formulation used in study 2308 is the same as that which is commercially available, and the fact that study 2308 was designed as a registration study and is of robust design and quality[2]. It should also be noted that the results of the other placebo-controlled studies (e.g. study 2203, which found no statistically significant difference between aliskiren 150mg and placebo in the reduction in msDBP (-1.69mmHg), and a reduction in msSBP of -2.14mmHg)[13] have not been as favourable to aliskiren as study 2308 (reduction in msDBP of -5.41 and msSBP of -9.3)[4]. The model is sensitive to the reduction in SBP that is assumed (see section 8.10.1)[2].

8.6.1.2 Additional analyses

In the first additional analysis, efficacy data are based on results of study 2308. The extent to which these results from a population of patients receiving aliskiren as a first-line treatment option are applicable to the population being modelled in the analysis (patients at step 4 of the NICE treatment guideline) is uncertain. The issues about the selective use of results from study 2308, discussed above, also apply to this analysis.

In the second of the additional analyses, efficacy data from an observational study conducted in primary care in the UK were used[2, 10]. In this study, 72 GP centres were surveyed and provided data on 223 patients who had been prescribed aliskiren for at least four weeks (184 patients taking aliskiren 150mg and 39 patients taking aliskiren 300mg daily). Aliskiren 150mg had been prescribed in 90 patients (49%) who had previously or were currently been prescribed a representative drug from all three classes of therapy recommended in steps 1 to 3 of the NICE treatment algorithm. In these patients (mSBP at baseline 172.45mmHg), the company submission reports a reduction from baseline in SBP of 17.25mmHg at four weeks, and a current reduction from baseline of 21.72mmHg (at last visit)][2, 10]. Both values have been tested as input parameters in this analysis.

It should be noted that there was no restriction placed on the centres taking part in these studies[2], and that few details are provided of those centres that provided or did not provide data. Uncontrolled, observational data of this kind is prone to several sources of bias, and should be interpreted with caution. The company submission states that it is believed that no selection bias had occurred, but given that this is data on file and few details are provided, none of the above data and information can be verified. The placebo response for this analysis has been taken to be that of the placebo response in the base case analysis, based on study 2308[2].

8.6.1.3 Non-CVD mortality

Non-CVD mortality is modelled as in the model developed for the NICE hypertension guideline[8]. Life tables for England and Wales and CVD-related deaths have been used to derive six-month probabilities of non-CVD related death based on five-year age bands between age 45 and 85 years[2].

8.6.2 Adverse events

It appears that adverse events have not been specifically considered in the model. The SPC notes that treatment with aliskiren in the clinical trials resulted in an overall incidence of adverse reactions similar to placebo at doses up to 300mg[1].

8.6.3 Utility weights

Health state utilities are taken from the model developed for the NICE hypertension guideline[8]. Data from a study that collected utility values from the HODaR database, which involves secondary care patients from Cardiff and Vales NHS Trust[31], are reportedly used to provide disutility associated with experiencing a CHD or stroke event, although the values assumed in the company submission are not immediately clear from the reference that is cited. In the base case analysis, there is no correction for age (i.e. patients without any CV events are assumed to have a utility value of 1.0).

8.7 Healthcare resource utilisation and cost

8.7.1 Drug costs

Specific drug costs in the model only include the costs of aliskiren. The comparator arm in each analysis is placebo, which is assumed to have no costs, and any other antihypertensive agents being taken are assumed to have the same costs in both the aliskiren and placebo arms[2]. Any modelled improvement in survival with aliskiren treatment would be associated with greater costs of additional antihypertensive agents in the aliskiren arm, but the company assumes that these will have a negligible effect on the model outputs[2].

8.7.2 Adverse event costs

Adverse events are not specifically included in the model.

8.7.3 Other resource use and costs

Costs associated with the different health states are based on those assumed in the model that was developed for the NICE hypertension guideline[8]. These have not been inflated from 2005 to 2008 costs[2].

8.8 Discounting

Costs and outcomes are discounted at 3.5% per annum[2], which is the preferred discount rate.

8.9 Results

Each analysis was performed by sampling from the baseline characteristics of age, SBP, HbA1c, body mass index (BMI), and total and HDL cholesterol values. Each run

involved 40,000 simulations and the mean results reported. The distributions describing each of these baseline characteristics have not been defined.

8.9.1 Primary base-case analysis – first-line use of aliskiren compared with placebo

In the base case analysis, with SBP reduction from baseline of 13.04mmHg for aliskiren 150mg daily and 3.77mmHg for placebo in patients receiving first-line treatment, the incremental cost per quality-adjusted life-year (QALY) gained for aliskiren compared to placebo is reported to be £25,855. This is based on additional costs of £3,740 (£8,653 aliskiren versus £4,913 placebo) and a gain of 0.145 QALYs (15.022 aliskiren versus 14.877 placebo)[2].

8.9.2 Additional analyses

8.9.2.1 First additional analysis – step 4 patient population using base case efficacy data

Changing the baseline characteristics of the modelled patients to reflect those of patients attending a Glasgow blood pressure clinic for step 4 treatment, but maintaining the efficacy of aliskiren observed in patients receiving first-line treatment (from study 2308), the incremental cost per QALY gained was estimated as £20,725, based on an increase in costs of £3,400 and a gain of 0.165 QALYs with aliskiren compared with placebo treatment[2].

8.9.2.2 Second additional analysis – step 4 patient population using efficacy of aliskiren from UK survey study

This analysis used two estimates of reduction from baseline in SBP with aliskiren, and assumed that the reduction with placebo would be the same as in the base case analysis[2]:

(i) 17.25mmHg reduction in SBP with aliskiren (observed at four weeks):-

The incremental cost per QALY gained is estimated to be £13,873, based on additional costs of £3,300 and a gain of 0.239 QALYs.

(ii) 21.72mmHg reduction in SBP with aliskiren (observed at last visit):-

The incremental cost per QALY gained is estimated to be £10,104, based on additional costs of £3,200 and a gain of 0.317 QALYs.

8.10 Sensitivity analysis

8.10.1 One-way sensitivity analyses

A range of one-way sensitivity analyses have been conducted around the scenarios of the base case and the additional analyses. In each of these, the model is most sensitive to the actual reduction achieved in SBP with aliskiren.

In the base case analysis, when the SBP reduction achieved was tested in the range 100% to 20% (13.04 to 5.62mmHg) of that observed in study 2308, the incremental cost per QALY gained ranged from £25,855 to £149,944. When tested at the same reduction as was achieved with placebo (i.e. assuming do difference in efficacy between placebo and aliskiren), placebo was less expensive and marginally more effective (i.e. placebo dominated aliskiren). In the additional analyses, in the step 4 patient populations, the same range of reductions in SBP have been tested. At a reduction in SBP with aliskiren of 80% of that observed in study 2308, the incremental cost per QALY gained increased to £25,664, and at 20% was £102,145. Under a scenario of no difference in efficacy between aliskiren and placebo, the incremental cost per QALY gained was in excess of £240,000. These finding are of relevance given that study 2308, used to provide the efficacy data for the base case analysis and the first additional analysis, was the most favourable to aliskiren; other placebo-controlled studies have found smaller differences in SBP reductions between aliskiren and placebo (e.g. study 2203 and study 2201 – see section 8.6.1.1).

Increasing or decreasing the baseline SBP by one standard deviation from the mean of 152.1mmHg used in the base case analysis (range 139.61mmHg to 163.61mmHg) had little impact on the model outputs. Between the ages of 42 and 63 years at baseline, the incremental cost per QALY ranged from £37,000 to £19,600. When health state utilities were adjusted for age, as per the model developed for the NICE clinical guideline, the incremental cost per QALY gained for the base case scenario increased to £33,500[2].

8.10.2 Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analysis has not been specifically carried out, although the model is probabilistic in the sense that each analysis was performed by sampling from the baseline characteristics of age, SBP, HbA1c, BMI, and total and HDL cholesterol values. Each run involved 40,000 simulations and the mean results have been reported. However, there are no confidence intervals around the mean estimates presented, and the combined impact of the range of parameter values tested in the one-way sensitivity analyses is not tested. There are no estimates of the probability of aliskiren being cost effective at particular thresholds of willingness to pay.

In relation to the base case analysis, it is reported that a reduction in SBP of 12mmHg is required to yield an incremental cost per QALY of £30,000. The company submission highlights that, in the survey study of UK GPs who prescribed aliskiren, a mean reduction of 17.24mmHg was seen in patients at step 4 of the NICE treatment algorithm. However, this finding, and those in all the sensitivity analyses above, does not negate the issues of appropriate comparators.

8.11 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of aliskiren.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

The budget impact analysis provided in the company submission relates to the use of aliskiren only at step 4 of the NICE treatment algorithm. In conducting the analysis, the company has reportedly used a patient record database that tracks patients from 150 GP practices in the UK (5% of which are Welsh practices) to determine the treatment of patients with hypertension. No details have been provided in relation to how these data have been scaled to provide estimates of the total number of patients with hypertension in Wales. These data have been used to estimate the number of patients that are uncontrolled on treatment, and specifically those who are uncontrolled on step 3 and step 4 drug regimens as defined by the NICE treatment guideline[8]. Company estimates of uptake in years 1 to 5 have been used to derive the number of patients expected to receive aliskiren. Only the aliskiren drug acquisition costs have been considered, and these have been weighted by the proportion of patients expected to take 150mg and 300mg daily doses. It is implicitly assumed that there will be no impact on market share of other antihypertensive agents.

9.2 Perspective and time horizon

The budget impact analysis is conducted from the perspective of NHS Wales and considers a time horizon of five years[2].

9.3 Data sources

9.3.1 Incident and prevalent cases

A patient record database that tracks patient records in 150 GP practices in the UK[6] (5% of which are Welsh practices) has reportedly been interrogated to provide estimates of the number of patients with hypertension and the proportion that are treated and are uncontrolled on treatment (assumed to be those with BP recorded as >140/90mmHg with diabetes and/or renal impairment, or those with BP >150/90mmHg). These estimates appear to have been scaled up to represent the numbers for Wales as a whole, but no details of how this has been done are presented. These data are not verifiable.

Based on these data, the company estimates that there are 453,135 patients in Wales with diagnosed hypertension, of which 83.4% are treated for essential hypertension. The total number of patients who are uncontrolled on step 3 treatments is estimated as 20,191, and the number who are uncontrolled on step 4 treatments is estimated as 6,985 in 2008[2]. It is assumed that the prevalence of hypertension increases by 4.8% each year (i.e. the incidence is estimated to 4.8% each year and for simplicity it has been assumed that no deaths/recovery occur). The total number of patients with uncontrolled hypertension on step 3 or step 4 regimens is estimated to be 28,473 in 2009, rising to 34,346 in 2013.

9.3.2 Projected rate of adoption and market share

Not all patients that are potentially eligible for aliskiren will receive this drug. Company estimates of these patient numbers have been confidentially provided.

No attempt has been made to estimate the impact on the market share of other agents at step 4 of the treatment algorithm.

9.3.3 Costs and resource use

Only the acquisition costs of aliskiren are considered in the analysis. The implicit assumption is that aliskiren would not replace any other agents. The company reports that data from a naturalistic study indicates that 76% of patients on aliskiren treatment take a dose of 150mg daily, and the remaining 24% take a dose of 300mg daily. This is presumably based on the results of two survey studies (one conducted in primary care, n=223; and one in secondary care n=37) [Data on file, Novartis][2]. These proportions are used to estimate the overall annual drug costs of aliskiren in each of years 2009 to 2013[2].

9.4 Results

Based on the assumption that aliskiren is restricted for use in Wales as an alternative option at step 4 of the NICE treatment algorithm; the company anticipates there would be no direct savings from the use of aliskiren. The acquisition costs of aliskiren are estimated to be around £152,000 in 2009, rising to around £664,000 in 2013[2].

9.5 Sensitivity analysis

No sensitivity analyses have been conducted for the budget impact estimates.

9.6 Table of comparative unit costs

The company submission focuses on the use of aliskiren at step 4 of the NICE treatment algorithm. Comparative costs of aliskiren and other agents recommended at

step 4 in the NICE treatment algorithm are provided in Table 1, along with examples of other drugs used in the management of hypertension.

Table 1. Comparative costs of aliskiren and other antihypertensive agents

Drug	Example daily dose[32]	28-day cost[32]
Aliskiren (renin inhibitor)	150mg 300mg	£19.80 £23.80
Examples of drugs recommended at step 4 of the NICE treatment algorithm[8]		
Atenolol (beta-blocker)	50mg	£0.30
Doxazosin (alpha-blocker)	1-16mg	£0.46-6.20
Examples of drugs recommended at steps 1-3 of the NICE treatment algorithm[8]		
Bendroflumethiazide (thiazide diuretic)	2.5mg	£0.40
Lisinopril (ACE inhibitor)	10-20mg	£0.76-1.31
Losartan (A2RA)	50mg	£12.80
Amlodipine (calcium-channel blocker)	5-10mg	£1.31
Doses shown above are for general comparison and do not imply therapeutic equivalence. ACE inhibitor = angiotensin converting enzyme inhibitor A2RA = angiotensin-II receptor antagonist		

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- Aliskiren is indicated for the treatment of essential hypertension[1]. It is the first in a new class of drugs; direct renin inhibitors; and may be suitable for prescribing within secondary or primary care if approved for use and experience in its prescribing is gained.

10.2 Related advice

- NICE and the National Collaborating Centre for Chronic Conditions, in conjunction with the British Hypertension Society (BHS) updated their clinical guidelines on the management of hypertension. These do not contain recommendations on the use of aliskiren, as these were prepared prior to its launch. In addition, NICE does not provide any guidelines on treatment of patients with Resistant Hypertension [8].
- Scottish Intercollegiate Guidelines Network (SIGN). Hypertension in older people, January 2001[33].
- Diabetes UK, the Royal College of Physicians and the Royal College of Nursing. Type 2 diabetes - management of blood pressure and blood lipids. Royal College of General Practitioners; October 2002[34].

10.3 Previous AWMSG/NICE advice

N/A

10.4 Ongoing studies

The company submission indicates that no new data for aliskiren in the treatment of essential hypertension is likely to become available within the next 6-12 months[2].

10.5 Patient organisation information

A patient organisation submission by the Blood Pressure Association and the British Hypertension Society was provided to NMG members.

GLOSSARY

Incidence:
The rate at which new cases occur in a population during a specified period[35].

Prevalence:
The proportion of a population that are cases at a point in time[35].

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Appendix 2. Additional Clinical Information

Table 1A. Phase III trial of aliskiren in patients with essential hypertension

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes
Aliskiren alone versus placebo						
2308 [9, 36]	Randomised double-blind, placebo controlled, phase III trial 8 week treatment period followed by a 2 week withdrawal period	833 enrolled 672 randomised to aliskiren 150mg, 300mg, 600mg or placebo ITT: 662 (included randomised patients with efficacy measurements at baseline and at least 1 measurement in the double-blind treatment period).	Male or non-pregnant, non-lactating female patients Aged ≥18 years Mild-moderate hypertension (defined as msDBP ≥95mmHg and <110mmHg) Patients with an absolute difference of ≤10mmHg in msDBP during last two visits of the single-blind placebo run-in period Those who provided written informed consent.	Mean age: 53 years 86.9% < 65 years 13.1% ≥ 65 years 61.6% male 61.3% Caucasian 62.2% BMI<30kg/m^2 37.1% BMI ≥ 30kg/m^2 msSBP/msDBP: 152.1/99.6mmHg	Aliskiren 150mg od (n=167) Aliskiren 300mg od (n=166) Aliskiren 600mg od (n=166) Placebo od (n=163) Previous antihypertensive treatment was withdrawn. Eligible patients entered a single blind, placebo run-in period of 2-4 weeks. Patients who fulfilled the criteria were randomised to one of the four treatment groups for an 8-week double blind treatment period. Patients were instructed to take study medication at approximately 8 AM daily, or after BP assessments on the morning of clinic visits. After the double blind treatment period patients entered a 2-week, treatment-free drug withdrawal period. Follow-up visits were conducted at 2, 4, 6, and 8 weeks during double blind treatment and 4 days and 2 weeks after withdrawal.	**Primary endpoint: Change in msDBP:** Aliskiren 150, 300 and 600mg were statistically superior to placebo in reducing msDBP at double-blind endpoint (LSM change from baseline: -10.33±0.63, -11.10±0.64, -12.52±0.64, -4.92±0.64, respectively). Pairwise comparison versus placebo: Aliskiren 150mg: -5.40±0.87; CI:-3.70, -7.11, p<0.0001 Aliskiren 300mg: -6.18±0.87; CI: -4.47, -7.88, p<0.0001 Aliskiren 600mg: -7.60±0.87; CI: -5.89, -9.30, p<0.0001 **Secondary endpoint:** **Change in msSBP:** Aliskiren 150, 300 and 600mg were statistically superior to placebo in reducing msSBP (LSM change from baseline: -13.04, -14.67, -15.83, -3.77, respectively; p<0.001). **Treatment Success*:** The proportion of patients achieving a successful treatment response was significantly higher with aliskiren compared to placebo (59.3%, 63.3% and 69.3% for 150, 300 and 600mg respectively, compared to 36.2% for placebo). **BP Control†:** BP control (BP <140/90mmHg) was significantly higher with aliskiren treatment compared to placebo (35.9%, 41.6% 46.4% and 20.3% in 150, 300, 600mg aliskiren and placebo, respectively). **ABPM:** Significant reductions were measured in 24-h ABPM for of aliskiren compared to placebo (p<0.0001). **RC and PRA Concentration:** Aliskiren 150, 300 and 600mg treatment for 8 weeks reduced PRA by 79.5%, 81.1% and 75%, respectively, whereas PRA increased by 19.5% in the placebo group. RC increased from baseline (51.4%, 101.6% and 228.5%, respectively), whilst it was almost unchanged in the placebo group.

ABPM: ambulatory BP monitoring; BMI: body mass index; BP: blood pressure; CI: confidence interval; ITT: intent-to-treat population; LSM: least squares mean; msDBP: mean sitting diastolic blood pressure; od: msSBP: mean sitting systolic blood pressure; once daily; PRA: plasma renin activity; RC: renin concentration
* Treatment Success= msDBP <90mmHg and/or reduction msDBP≥10mmHg
† BP Control=BP<140/90mmHg.

Appendix 2. Continued

Table 1b. Naturalistic Studies: Aliskiren therapy for treatment of essential hypertension at step 4

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment Groups	Outcomes
Primary Care						
[10]	Naturalistic data review An online survey collecting data from primary care clinicians experienced in the use of aliskiren in clinical practice	223 patients were reported 116 patients were included in the analysis (as they had received A/C/D treatment).	Patients treated with either 150mg or 300mg aliskiren for at least 4 weeks Patients treated with the A/C/D treatment algorithm either in the past or at the time of data collection.	Mean age: 62 years 46% male 86% Caucasian Mean BMI: 28kg/m^2 mSBP: 173.39mmHg 55% diabetes	Aliskiren 150mg (n=90) Aliskiren 300mg (n=26) Patients previously or currently treated using the A/C/D treatment algorithm received either aliskiren 150mg or aliskiren 300mg.	**Reduction in mSBP after 4 weeks:** Aliskiren 150mg: 17.25mmHg (4 non-responders) Aliskiren 300mg: 15.7mmHg (2 non-responders) **Last recorded reduction in mSBP:** Aliskiren 150mg: 21.72mmHg (2 non-responders) Aliskiren 300mg: 26.73mmHg (0 non-responders) 94 (51%) patients in the aliskiren 150mg were not included for analysis as they had not previously received A/C/D treatment 13 (50%) patients in the aliskiren 300mg were not included for analysis as they had not previously received A/C/D treatment.
Secondary Care						
[11]	Naturalistic data review 13 UK hospitals were identified as centres who had experience of prescribing aliskiren and secondary care clinicians were asked to complete a survey	37 patients were reported 22 patients were included in the analysis (as they had received A/C/D treatment).	Patients treated with either 150mg or 300mg aliskiren for at least 4 weeks Patients treated with the A/C/D treatment algorithm either in the past or at the time of data collection.	Mean age: 65 years 60% male 90% Caucasian Mean BMI: 31kg/m^2 mSBP: 170.77mmHg 44% diabetes	Aliskiren 150mg (n=3) Aliskiren 300mg (n=19) Patients previously or currently treated using the A/C/D treatment algorithm received either aliskiren 150mg or aliskiren 300mg.	**Reduction in mSBP after 4 weeks:** Aliskiren 150mg: 27mmHg (0 non-responders) Aliskiren 300mg: 11mmHg (4 non-responders) 4 (57%) patients in the aliskiren 150mg were not included for analysis as they had not previously received A/C/D treatment 11 (37%) patients in the aliskiren 300mg were not included for analysis as they had not previously received A/C/D treatment.

BMI: body mass index; mSBP: mean systolic blood pressure.
A/C/D treatment algorithm= patients will have been prescribed an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) (A), calcium channel blocker (CCB) (C), and diuretic (D) in the past or currently as deemed appropriate by their clinician. Non-responder=had no change or rise in SBP.