Australian Government

Department of Health and Ageing

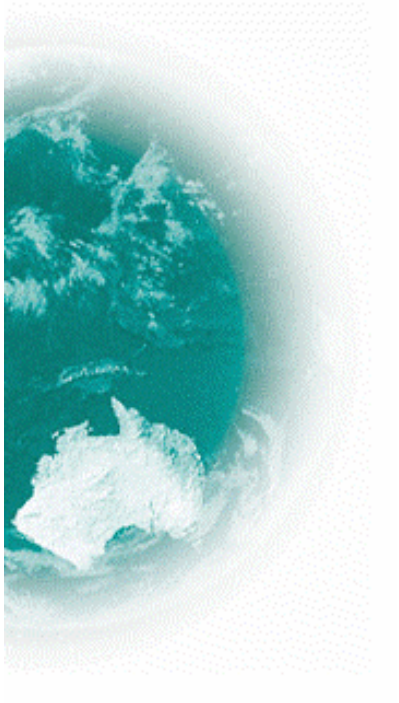
Therapeutic Goods Administration

Australian Public Assessment Report
for
Aliskiren (as hemifumarate)/Hydrochlorothiazide

Proprietary Product Name: Rasilez HCT/Enviage HCT

Submission No: PM-2008-2072-3

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd



March 2010

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	New fixed combination
Decision:	Approved
Date of Decision	5 February 2010
Active ingredient(s):	Aliskiren (as hemifumarate)/ Hydrochlorothiazide
Product Name(s):	Rasilez HCT/Enviage HCT
Sponsor's Name and Address	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road North Ryde NSW 2113
Dose form(s):	Film-coated tablets
Strength(s):	150 mg/12.5 mg of Aliskiren/Hydrochlorothiazide 150 mg/25 mg of Aliskiren/Hydrochlorothiazide 300 mg/12.5 mg of Aliskiren/Hydrochlorothiazide 300 mg/25 mg of Aliskiren/Hydrochlorothiazide
Container(s):	Aclar/ PVC//Al or PA/Al/PVC//Al Blisters
Pack size(s):	7, 14, 28, 30, 49, 50, 56, 90, 98 and 280 tablets
Approved Therapeutic use:	Treatment of hypertension. Treatment should not be initiated with these fixed dose combinations.
Route(s) of administration:	Oral
Dosage:	One tablet daily

Product Background

Hypertension has been identified as a major risk factor for cardiovascular diseases such as stroke, myocardial infarction, and heart failure. It is widely recognised that an adequate control of hypertension is important to significantly decrease cardiovascular mortality and morbidity. For most hypertensive patients, the management of hypertension with a general target blood pressure (BP) of < 140/90 mm Hg is recommended. A lower BP target (<130/80 mm Hg) is recommended in high-risk patient populations, such as those with target organ damage, diabetes, or renal disease.

Several therapeutic choices are currently available to lower blood pressure, including diuretics, β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB) and calcium channel antagonists.

The inhibition of the renin-angiotensin system (RAS) is an effective way to intervene in the pathogenesis of cardiovascular and renal disorders. Renin is the enzyme responsible for the conversion of angiotensinogen to angiotensin I. Then the angiotensin converting enzyme (ACE) transforms angiotensin I into the active octapeptide angiotensin II, which acts via type-1 angiotensin II receptors (AT1) to increase arterial tone, adrenal aldosterone secretion, renal sodium reabsorption, sympathetic neurotransmission, and cellular growth. Some of currently used antihypertensive drugs intervene at different points of the renin-angiotensin system, for example β-blockers, ACE -inhibitors, angiotensin-receptor antagonists or renin-inhibitors. Despite the availability of several therapeutic choices, not all hypertensive patients achieve adequate control of blood pressure with a single antihypertensive drug. For many patients a combination of two or more

antihypertensive medications may be required to reach adequate blood pressure control. Thus, the development of fixed-dose combinations of different antihypertensive drugs may help to improve patient compliance over the free combination of the single monotherapies and might contribute to the improvement of their safety profile.

Aliskiren is an orally active, non-peptide inhibitor of renin. Renin is secreted by the kidney in response to decreases in blood volume and in renal perfusion. This response initiates a cycle that includes the renin angiotensin system (RAS) and a homeostatic feedback loop. All agents that inhibit this system, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentration. During treatment with aliskiren, the feedback loops are neutralized. As a result, plasma renin, plasma renin activity, angiotensin I and angiotensin II are all reduced, whether aliskiren is used as monotherapy or in combination with other anti-hypertensive agents.

At its 257th meeting on 04 April 2008, the Australian Drug Evaluation Committee (ADEC) recommended approval of a submission from Novartis Pharmaceuticals Pty Ltd to register the trade names Rasilez and Enviage film-coated tablets, both containing the new chemical entity aliskiren 150 mg and 300 mg. The ADEC also recommended that such approval should be conditional upon the sponsor commencing a clinical outcome study in patients with hypertension to the satisfaction of the TGA, within 2 years of registration. The latter was made a condition of registration.

Hydrochlorothiazide (HCTZ) is a well-known thiazide diuretic commonly used for the treatment of hypertension, due to its effect on volume and sodium depletion. Hydrochlorothiazide inhibits the active reabsorption of sodium, mainly in the distal kidney tubules and promotes the excretion of sodium, chloride and water. The renal excretion of potassium and magnesium increases dose-dependently, while calcium is reabsorbed to a greater extent. Hydrochlorothiazide decreases plasma volume and extracellular fluid and reduces cardiac output and blood pressure. During long-term therapy, reduced peripheral resistance contributes to the blood pressure reduction. Hydrochlorothiazide is used as monotherapy and in combination with other antihypertensive medicinal products such as angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers and β-blockers.

This submission is to register new fixed-dose combination tablets which contain 150 mg or 300 mg of aliskiren (as hemifumarate) and 12.5 mg or 25 mg of hydrochlorothiazide. The proposed indicated is for:

Treatment of hypertension:

- *The initial treatment of hypertensive patients unlikely to achieve control of blood pressure with a single agent*
- *In patients whose blood pressure is not adequately controlled on monotherapy*
- *As replacement therapy in patients already receiving aliskiren and hydrochlorothiazide from separate tablets at the same dose levels.*

Regulatory Status at the Time of Submission

Monotherapy tablets containing 150 mg and 300 mg aliskiren (as hemifumarate) were registered in Australia by Novartis Pharmaceuticals (Novartis) in June 2008 with the brand names Rasilez and Enviage (AustR 134567, 134570, 134571, 134572). They are indicated for the 'treatment of hypertension'. There are no generic products.
Monotherapy tablets containing the diuretic hydrochlorothiazide tablets have been registered for many years for the use in the treatment of hypertension and there are a number fixed dose combination tablets using this drug substance. Novartis have registered a hydrochlorothiazide

combination tablet with valsartan containing 12.5 or 25 mg of hydrochlorothiazide (Co-Diovan tablets: AustR 96740, 96741, 96742, 135782 and 135812).

A similar application to the present Australian application has been approved in the US (18 January 2008), the European Union (19 January 2009), Canada (4 September 2009), and Switzerland (28 October 2008).

In the US, the product is registered as Tekturna HCT. The indication for usage is as follows:

Tekturna HCT is indicated for the treatment of hypertension.

Both aliskiren and hydrochlorothiazide are associated with dose-dependent and dose-independent adverse effects. Patients treated with Tekturna HCT may experience any or all of these adverse effects. For dose-dependent adverse effects, using a strength of Tekturna HCT with a lower dose of the component suspected of causing the adverse effect may produce better tolerability.

Add-On Therapy

A patient whose blood pressure is not adequately controlled with aliskiren alone or hydrochlorothiazide alone may be switched to combination therapy with Tekturna HCT.

A patient whose blood pressure is controlled with hydrochlorothiazide alone but who experiences hypokalemia may be switched to combination therapy with Tekturna HCT.

A patient who experiences dose-limiting adverse reactions on either component alone may be switched to Tekturna HCT containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions.

Replacement Therapy

Tekturna HCT may be substituted for the titrated components.

With the recent removal of the restriction below, the product is now available as initial therapy.

(Limitation of Use

This fixed dose combination is not indicated for initial therapy.)

In the EU, the indication is as follows:

in the treatment of essential hypertension in adults, when Rasilez HCT is indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone or when indicated as a substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination

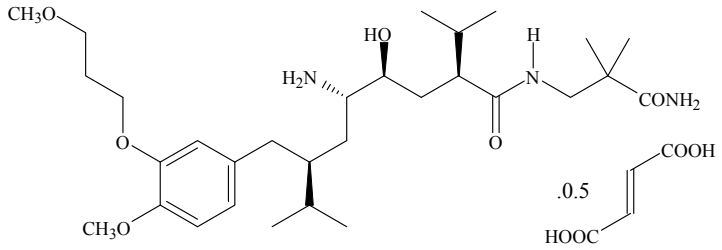
Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Aliskiren hemifumarate is the hemifumarate salt of aliskiren. The specifications of the aliskiren hemifumarate (but not the route of manufacture) have been updated since the registration of the aliskiren monotherapy tablets. The updates were all improvements including the addition of a test and limit for a genotoxic intermediate.



aliskiren hemifumarate

***Chemical Name*:**

((2*S*,4*S*,5*S*,7*S*)-N-(2-carbomoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxyropoxy)phenyl]octanamide hemifumarate

CAS Number: [173334-58-2] ([173334-57-1] for free base)

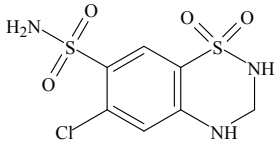
Molecular Formula: $C_{30}H_{53}N_3O_6.½C_4H_4O_4$

Molecular Weight: 609.4 (551.8 for free base)

Description: A white to slightly yellowish white powder

Solubility in Water: Freely soluble >350 mg/mL (35 %w/v) over pH range 4.2-7.0

Drug Master Files for HCTZ were provided. Details relating to these materials were evaluated during the evaluation of Novartis' submission to register their "Co-Diovan" products. There have been minor (and acceptable) changes in relation to one of the supplier's material since that submission.



hydrochlorothiazide

***Chemical Name*:**

6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide

CAS Number: [58-93-5]

Molecular Formula: $C_7H_8ClN_3O_4S_2$

Molecular Weight: 297.7

Description: A white to almost white powder

Solubility in water: Very slightly soluble (~0.6 mg/mL, 0.06 %w/v) over pH range 1.0-7.4

Drug Product

The tablets are to be manufactured by Novartis. The tablets contain no unusual excipients and the quality of the excipients is adequately controlled. The lactose used in the tablets is from an acceptable source. The tablets are all the same shape, they are distinguished by size, colour and markings, and by different colour packagings. The tablets are well controlled with satisfactory expiry limits and release limits that allow for the changes observed on storage. Stability data was provided to support the proposed shelf lives of 18 months when stored below 30ºC in opaque PA/Al/PVC //Al blister packs. The storage conditions 'protect from moisture' and 'protect from light' also apply.

Bioavailability

The pivotal Phase III efficacy studies were performed with co-administration of single entity aliskiren tablets and hydrochlorothiazide capsules.

- The same 12.5 mg and 25 mg hydrochlorothiazide capsules were used throughout the efficacy studies and in the bioavailability studies.
- The registered 150 mg aliskiren tablet was not used in all of the efficacy studies as sometimes an overcapsulated tablet was used, but equivalence of the formulations used has previously been established in the earlier submission to register the aliskiren monotherapy tablets which gave equivalence of serum area under the curve (AUC), but not maximal plasma concentration (C_{max}) (90% CI = 0.70-0.90, this was accepted by the Delegate).
- The registered 300 mg aliskiren tablet was not used in all of the efficacy studies: the only difference was that the tablets in some studies had a different film-coat. The company has previously submitted a justification for not providing bioavailability data comparing these two formulations and this has been accepted.

Four bioavailability studies were provided together with a justification for not providing other bioavailability data. Appropriately validated test methods for the determination of aliskiren and hydrochlorothiazide were used in the bioavailability studies.

Study SPH100A 2101

In a 2-way cross-over, this study compared the relative bioavailability of the proposed "150/25" tablet to the bioavailability from a dose consisting of the (overcapsulated) registered 150 mg aliskiren tablet and an overseas-sourced 25 mg hydrochlorothiazide capsule.

Table 11-4 Bioequivalence results for aliskiren and HCTZ pharmacokinetic parameters following single oral doses of SPH100 (aliskiren 150 mg/HCTZ 25 mg) in fixed combination tablet (Test) or aliskiren 150 mg overencapsulated tablet and HCTZ 25 mg capsule as free combination (Reference) to healthy subjects (N=70)

Pharmacokinetic Parameter	Adjusted geometric means		Ratio of geometric means	
	Test [a]	Reference [a]	Estimate	90% Confidence Interval
		Aliskiren		
C_{max} (ng/mL)	79.06	79.53	0.99	0.87 – 1.14
AUC_{0-last} (h*ng/mL)	429.00	428.51	1.00	0.92 – 1.09
AUC_{0-inf} (h*ng/mL)	487.72	480.45	1.02	0.92 – 1.12
		HCTZ		
C_{max} (ng/mL)	168.33	174.52	0.96	0.93 – 1.00
AUC_{0-last} (h*ng/mL)	1100.7	1138.1	0.97	0.94 – 0.99
AUC_{0-inf} (h*ng/mL)	1135.0	1169.2	0.97	0.95 – 1.00

[a]: Test: SPH100 (aliskiren 150 mg/HCTZ 25 mg) fixed combination tablet (Treatment 1); Reference: aliskiren 150 mg tablet and HCTZ 25 mg hard gelatin capsule as free combination (Treatment 2)

Source: Section 14 Table 14.2-1.1.

The results (see above) indicate that the pharmacokinetic profiles of aliskiren and hydrochlorothiazide from the proposed "150/25" fixed dose combination tablet are bioequivalent to those from the co-administration of a separate 150 mg aliskiren tablet (registered) and a 25 mg hydrochlorothiazide capsule sourced overseas.

Study SPH100A 2102

In a 2-way cross-over, this study compared the relative bioavailability of the proposed "300/12.5" tablet to the bioavailability from a dose consisting of the registered 300 mg aliskiren tablet and an overseas-sourced 12.5 mg hydrochlorothiazide capsule.

Table 11-4 Bioequivalence results for aliskiren and HCTZ pharmacokinetic parameters following single oral doses of SPH100 (aliskiren 300 mg/HCTZ 12.5 mg) in fixed combination tablet (Test) or aliskiren 300 mg tablet and HCTZ 12.5 mg capsule as free combination (Reference) to healthy subjects (N=70)

Pharmacokinetic Parameter	Adjusted geometric means		Ratio of geometric means	
	Test [a]	Reference [a]	Estimate	90% Confidence Interval
		Aliskiren		
C_{max} (ng/mL)	166.00	188.27	0.88	0.75 – 1.04
AUC_{0-last} (h*ng/mL)	1117.3	1205.3	0.93	0.86 – 1.00
AUC_{0-inf} (h*ng/mL)	1226.6	1309.2	0.94	0.87 – 1.01
		HCTZ		
C_{max} (ng/mL)	71.94	81.58	0.88	0.85 – 0.92
AUC_{0-last} (h*ng/mL)	474.56	520.44	0.91	0.88 – 0.94
AUC_{0-inf} (h*ng/mL)	512.89	558.91	0.92	0.89 – 0.94

[a]: Test: SPH100 (aliskiren 300 mg/HCTZ 12.5 mg) fixed combination tablet (Treatment 1); Reference: aliskiren 300 mg tablet and HCTZ 12.5 mg hard gelatin capsule as free combination (Treatment 2)

Source: Section 14 Table 14.2-1.1.

The results (see above) indicate that the pharmacokinetic profiles of aliskiren and hydrochlorothiazide from the proposed "300/12.5" fixed dose combination tablet are bioequivalent to those from the co-administration of a separate 300 mg aliskiren tablet (registered) and a 12.5 mg hydrochlorothiazide capsule sourced overseas, except with respect to C_{max} for aliskiren. This was brought to the attention of the Delegate.

Study SPH100A 2103

In a 2-way cross-over, this study compared the relative bioavailability of the proposed "300/25" tablet to the bioavailability from a dose consisting of the registered 300 mg aliskiren tablet and an overseas-sourced 25 mg hydrochlorothiazide capsule.

The results (see below) indicate that the pharmacokinetic profiles of aliskiren and hydrochlorothiazide from the proposed "300/25" fixed dose combination tablet are bioequivalent to those from the co-administration of a separate 300 mg aliskiren tablet (registered) and a 25 mg hydrochlorothiazide capsule sourced overseas.

Table 11-4 Bioequivalence results for aliskiren and HCTZ pharmacokinetic parameters following single oral doses of SPH100 (aliskiren 300 mg/HCTZ 25 mg) in fixed combination tablet (Test) or aliskiren 300 mg tablet and HCTZ 25 mg capsule as free combination (Reference) to healthy subjects (N=70)

Pharmacokinetic Parameter	Adjusted geometric means		Ratio of geometric means	
	Test [a]	Reference [a]	Estimate	90% Confidence Interval
		Aliskiren		
C_{max} (ng/mL)	233.71	247.34	0.94	0.82 – 1.08
AUC_{0-last} (h*ng/mL)	1156.32	1266.99	0.91	0.83 – 1.00
AUC_{0-inf} (h*ng/mL)	1271.81	1392.98	0.91	0.83 – 1.00
		HCTZ		
C_{max} (ng/mL)	140.45	157.86	0.89	0.85 – 0.93
AUC_{0-last} (h*ng/mL)	961.90	1037.95	0.93	0.89 – 0.96
AUC_{0-inf} (h*ng/mL)	995.33	1075.78	0.93	0.89 – 0.96

[a]: Test: SPH100 (aliskiren 300 mg/HCTZ 25 mg) fixed combination tablet (Treatment A); Reference: aliskiren 300 mg tablet and HCTZ 25 mg hard gelatin capsule as free combination (Treatment B)

Source: Section 14 Table 14.2-1.1.

Study SPH100A 2104

In a 2-way cross-over, this study determined the effect of food on the proposed "300/25" tablet.

Table 11-4 Bioequivalence results for aliskiren and HCTZ pharmacokinetic parameters following single oral doses of SPH100 (aliskiren 300 mg/HCTZ 25 mg) SPH100 (aliskiren 300 mg/HCTZ 25 mg) under fed and fasted conditions to healthy subjects (N=30)

Pharmacokinetic Parameter	Adjusted geometric means		Ratio of geometric means	
	Test [a]	Reference [a]	Estimate	90% Confidence Interval
		Aliskiren		
C_{max} (ng/mL)	39.16	213.81	0.18	0.14 – 0.24
AUC_{0-last} (hr•ng/mL)	457.52	1204.74	0.38	0.33 – 0.44
AUC_{0-inf} (hr•ng/mL)	522.25	1312.96	0.40	0.34 – 0.46
		HCTZ		
C_{max} (ng/mL)	153.98	136.59	1.13	1.06 – 1.20
AUC_{0-last} (hr•ng/mL)	1103.80	978.07	1.13	1.06 – 1.20
AUC_{0-inf} (hr•ng/mL)	1143.27	1011.82	1.13	1.07 – 1.20

[a]: Test: Fed (Treatment 1); Reference: Fasted (Treatment 2)

Source: Section 14 Table 14.2-1.1

The results (see above) indicated that food does not affect the bioavailability of hydrochlorothiazide from the fixed-dose combination tablets, but it reduces the bioavailability of aliskiren. There is a 60% drop in AUC and an 80% drop in C_{max}. These changes are similar to those for the monotherapy tablets. This was brought to the attention of the Delegate.

Justifications submitted for non-supply of bioavailability/bioequivalence data

No bioavailability data has been provided comparing the proposed "150/12.5" tablet to either of the proposed "300/25" tablet or to a dose consisting of a 150 mg aliskiren tablet and a 12.5 mg hydrochlorothiazide tablet. A justification for this omission was provided. The chemistry and quality control aspects, and the clinical aspects, were acceptable.

The sponsor has also provided a justification for using the overseas hydrochlorothiazide capsules in these studies rather than hydrochlorothiazide tablets or capsules available in Australia. In part this referred to the previous submission to register "Co-Diovan" tablets. That justification was relevant to this submission and acceptable.

Other bioavailability comments

No data was included in this submission in relation to whether there are any pharmacokinetic interactions between aliskiren and hydrochlorothiazide. The sponsor justified this by referring to data provided in the submission to register the aliskiren monotherapy tablets. This indicates no change to the AUCs, but that the C_{max} results are lowered (for aliskiren this was 78% and for hydrochlorothiazide 74%).

No data on the absolute bioavailability of the tablets has been provided. However, given the results of the studies provided, it will be accepted that results for the proposed fixed-dose combination tablets are similar to those for the relevant monotherapy tablets.

Previous Consideration by the Pharmaceutical Subcommittee of ADEC (PSC)

Details of this submission were presented at the 128th meeting of the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (ADEC) in September 2009. The PSC endorsed all question raised by the quality evaluator and in particular the question raised in relation to the reported haemolysis in a number of the subject plasma samples. The PSC had no objections to approval of these products provided all issues were addressed to the satisfaction of the TGA. This was the case. In relation to the haemolysis, the number of instances was such that they did not affect the conclusions of the studies.

Quality Summary and Conclusions

Approval of the application was recommended with respect to chemistry and quality control.

With respect to bioavailability, data was provided (in this or earlier submissions):

- That is purported to demonstrated bioequivalence of aliskiren and hydrochlorothiazide when administered as the combination aliskiren (as hemifumarate) and hydrochlorothiazide tablets to aliskiren and hydrochlorothiazide when administered as a co-administration of aliskiren (as hemifumarate and hydrochlorothiazide monotherapy tablets. This was the case for most of the studies provided, but in one case C_{max} was lowered.
- That shows that food causes a large decrease in the bioavailability of aliskiren, but has no effect on hydrochlorothiazide, when aliskiren and hydrochlorothiazide are administered as the combination aliskiren (as hemifumarate) and hydrochlorothiazide tablets.
- That there is a pharmacokinetic interaction between aliskiren and hydrochlorothiazide in that co-administration causes a decrease in the C_{max} of both compared to single administration of each drug substance.

The sponsor has stated that these observations are clinically unimportant.

III. Nonclinical Findings

Introduction

The nonclinical data dossier was limited to four analytical methods/validation reports and two repeat dose toxicity studies (2 and 13 weeks) in rats utilising various aliskiren/hydrochlorothiazide (HCTZ) combinations. The pharmacokinetic validation studies were generally not GLP compliant. The longer-term, 13 week repeat dose toxicity study was GLP compliant.

The nonclinical data requirements for a fixed combination are noted in two Australian adopted, European Union (EU) guidelines. [1,2] Nonclinical studies are generally not required when there is sufficient, well-documented clinical experience to establish all aspects of clinical efficacy and safety.[3] The toxicity profile for HCTZ has been well characterised alone and in combination with a number of registered products. However, while other renin-angiotensin-aldosterone system (RAAS) inhibitors have had fairly considerable clinical experience, aliskiren has only recently been registered for use in Australia since June 2008 and the USA since March 2007, and is the first drug in its class (renin inhibitor). Thus, there were greater data expectations with the proposed new combination.

The nonclinical overview provided by the sponsor did not discuss the genotoxic or carcinogenic potential, or the reproductive and developmental toxicity of the combination product. With a very

[1] CPMP/SWP/799/95. Guideline on the non-clinical documentation for mixed marketing authorisation applications
[2] CPMP/SWP/258498/2005. Guideline on the non-clinical development of fixed combinations of medicinal products
[3] Section 2.1. CPMP/SWP/799/95

limited nonclinical data dossier for the combination product, the potential for additive or synergistic toxicity effects could only be extrapolated from the individual toxicities of aliskiren and HCTZ. Where possible, the nonclinical evaluator has attempted to allay safety concerns arising from the absence of empirical data for the combination product, but greater weight of evidence may have to depend on the clinical data.

Pharmacology

Primary pharmacodynamics

No new nonclinical pharmacodynamic data were submitted. Efficacy claims for the combination will therefore be reliant on the clinical data. The rationale for combining a renin inhibitor (aliskiren) with a thiazide diuretic (HCTZ) was supported by clinical findings indicating greater blood pressure control with the combination product than the individual components alone. While the use of HCTZ results in natriuresis and blood volume reduction, it also stimulates renin release. The stimulation of RAS/RAAS limits the antihypertensive effects of the diuretic. Concomitant administration of a RAAS blocker such as aliskiren has been shown to counteract the HCTZ-induced increase in plasma renin activity (PRA). A similar rationale for the combined use with HCTZ has also supported the registration for HCTZ combined with angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor antagonists (ARA).

Pharmacokinetics

Assays were validated for the analysis of aliskiren in human and rodent plasma, and HCTZ in human plasma. There were no studies investigating the effect of HCTZ on aliskiren plasma protein binding or potential pharmacokinetic interactions.

Theoretically, given that HCTZ is confined to red blood cells (Beermann *et al*, 1976) and has low plasma protein binding (40-60%) (Colussi *et al*, 1977), and similarly aliskiren protein binding in humans is also about 50%, the potential for either aliskiren or HCTZ to affect the pharmacokinetics of each other is considered minimal. Furthermore, as HCTZ is not metabolised to any great extent with the bulk of the dose excreted unchanged in urine (Beermann *et al*, 1976; Beermann & Groschinsky-Grind, 1977), and that no relevant pharmacokinetic interactions have been reported between HCTZ and other drugs especially via CYP450 enzymes (Kroner, 2002), no significant interactions would be expected with aliskiren. Nevertheless, there appears to be some interaction between aliskiren and HCTZ. Clinically, aliskiren C_{max} and AUC values were reduced by 25% and 4%, respectively, in the presence of HCTZ; and HCTZ C_{max} and AUC values were reduced by 25% and 10%, respectively, in the presence of aliskiren. In nonclinical studies, rat plasma toxicokinetic analysis revealed a reduction in aliskiren C_{max} and AUC values in the presence of HCTZ, but an increase in HCTZ C_{max} and AUC values in the presence of aliskiren (see further discussion below regarding relative exposure). It may be prudent for the sponsor to explain the mechanism of action of this effect on aliskiren and HCTZ plasma toxicokinetics.

Relative exposure

The proposed clinical formulations of aliskiren and HCTZ were generally in the ratio of 12:1 (150/12.5 mg and 300/25 mg), although lower (6:1, 150/25 mg) and higher (24:1, 300/12.5 mg) aliskiren dose ratios were also proposed for registration.

Toxicokinetic analysis of aliskiren in rats revealed a reduction in plasma C_{max} (by 42% in males and by 28% in females) and AUC (by 54% in males and by 45% in females) when combined with HCTZ (150mg aliskiren + 12 mg/kg HCTZ) compared with aliskiren (150 mg/kg) alone. The dosing ratio in this combination (about 12:1) was equivalent to that proposed for use clinically.

On the other hand, there was an increase in HCTZ plasma C_{max} (by 25% in males and by 51% in females) and AUC (by 53% in males and by 58% in females) when co-administered with aliskiren (12 mg HCTZ + 150 mg aliskiren) compared with HCTZ alone (12 mg). Exposure to both products,

whether alone or in combination at the high dose (150/12 mg/kg), was greater in female than male rats.

When aliskiren and HCTZ were administered to humans as a fixed combination (300 mg/25 mg), plasma C_{max} values for both aliskiren and HCTZ were reduced by about 25%, and plasma AUC values for aliskiren and HCTZ were reduced by 4% and 10%, respectively compared with monotherapy (aliskiren 300 mg; HCTZ 25 mg).

The calculation of the relative animal-to-human exposure ratios based on plasma C_{max} and AUC values required the correction for the varying levels of unbound (free) aliskiren in rat and human plasma – see Table 1 for details. In the absence of any information indicating species-dependent plasma protein binding for HCTZ, exposure margins for HCTZ have been calculated assuming negligible differences between rats and humans – see Table 2 for details.

Table 1: Relative animal to human exposure to unbound plasma aliskiren in rodent combination product toxicity studies

Study	**Dose** [a] **(mg/kg/day)**	**C_{max} (ng/mL) - total**	**ER_{Cmax}** [b] **(Free)**	**AUC_{0-24h} (ng.h/mL) - total**	**ER_{AUC}** [b] **(Free)**
Rat - 2 week **0670321**	30/2.5, 100/8	M: 33.9, 169	0.08, 0.4	M: 66.1, 567	0.02, 0.2
		F:27.3, 508	0.07, 1.2	F: 62.8, 560	0.02, 0.2
Rat - 13 week **0670118**	50/4, 100/8, 150/12	M: 8.06, 24.0, 108	0.02, 0.06, 0.3	M: 57.8, 185, 351	0.02, 0.06, 0.12
		F: 7.67, 140, 138	0.02, 0.3, 0.3	F: 45.6, 406, 478	0.02, 0.14, 0.16

[a] Dose = aliskiren/HCTZ.

[b] Human comparative data for aliskiren (*free* + *bound*): C_{max}: 309 ng/mL; AUC_T 2210 ng.h/mL for Aliskiren 300 mg/HCTZ 25 mg. Correcting for the proportion of unbound aliskiren in human plasma (0.50), the comparative clinical PK values are for *free* aliskiren: C_{max}: 154.5 ng/mL; AUC_T 1105 ng.h/mL. The exposure ratio is further corrected for the proportion of *free* aliskiren in rat plasma, 0.38. The levels of unbound aliskiren in plasma have previously been determined .

Table 2: Relative animal to human exposure to plasma HCTZ in rodent combination product toxicity studies

Study	**Dose** [a] **(mg/kg/day)**	**C_{max} (ng/mL)**	**ER_{Cmax}** [b]	**AUC_{0-24h} (ng.h/mL)**	**ER_{AUC}** [b]
Rat - 2 week **0670321**	30/2.5, 100/8	M: 321, 840	1.7, 4.5	M: 1310, 3490	1.0, 2.7
		F: 422, 828	2.3, 4.4	F: 1310, 3080	1.0, 2.4
Rat - 13 week **0670118**	50/4, 100/8, 150/12	M: 352, 854. 1070	1.9, 4.6, 5.7	M: 2040, 5500, 6100	1.6, 4.3, 4.8
		F: 570, 863, 1320	3, 4.6, 7.1	F: 2160, 4110, 7250	1.7, 3.2, 5.7

[a] Dose = aliskiren/HCTZ.

[b] Human comparative data for HCTZ: C_{max}: 187 ng/mL; AUC_T 1273 ng.h/mL for Aliskiren 300 mg/HCTZ 25 mg.

Toxicology

Repeat dose toxicity studies in animals were conducted using a dose ratio of aliskiren to HCTZ of 12 to 12.5:1 which was equivalent to that proposed for use in humans. Plasma toxicokinetic data, however, indicated that the maximum tolerated dose of up to 150/12 mg/kg/day (13 weeks, orally) in rats resulted in exposure margins for aliskiren C_{max} and AUC that were less than that expected clinically with the highest dose combination of 300/25 mg/day. On the other hand, plasma toxicokinetics of HCTZ indicated exposure margins for HCTZ C_{max} and AUC that were 1- to 7-fold that expected clinically. Higher doses of aliskiren/HCTZ in rats, 300/25 mg/kg/day, were associated with moribundity that led to the early sacrifice of these treated animals.

The key pathological finding from the 13-week repeat dose toxicity study in rats was an increase in adrenal gland vacuolation of the zona glomerulosa. This effect on adrenal glands was not reported previously with aliskiren and may be related to HCTZ administration. Similar gastrointestinal changes to that reported with aliskiren were also seen in the current studies, albeit at a lower incidence and severity. Interestingly, there appeared to be a reduction in the morbidity and mortality in the new 13 week study related to the gavage procedure compared with that previously reported in rats with aliskiren alone, for example the 13 week repeat dose toxicity study. This may have been the result of improved administration technique and has little clinical consequence.

It would appear that the toxicity findings with the use of the combination product are dominated by the dose limiting effects of HCTZ more that aliskiren. As the toxicokinetic analysis revealed in the 13 week repeat dose toxicity study, HCTZ plasma C_{max} and AUC values were increased with the use of the combined aliskiren/HCTZ formulation. In humans, however, this effect on exposure is reversed for HCTZ. Thus it is unclear whether the toxicity findings in these nonclinical studies are directly comparable to the clinical setting.

Studies not conducted

The sponsor has not provided any empirical data for the effects of HCTZ alone or in combination with aliskiren on:

- Safety pharmacology;
- Pharmacokinetic interactions;
- Genotoxicity;
- Carcinogenicity; or
- Reproductive toxicity

In the absence of these data, the toxicity profile of the combination product can only be extrapolated from data obtained for aliskiren alone and what is in the public domain for HCTZ.

Carcinogenic potential of aliskiren

Aliskiren was not mutagenic in bacterial and mammalian cell gene mutation assays *in vitro* and did not induce chromosomal aberrations *in vitro* or *in vivo*.

The carcinogenic potential of aliskiren was assessed in a 2-year study in rats and a 6 month study in TgrasH2 mice. A maximum dose of 1500 mg/kg/day of aliskiren was given in the diet of both studies. In mice, the incidence of hemangioma in the spleen, kidneys and femur/marrow (4% in 25 mice) were slightly higher that the concurrent controls (0% in 25 mice) and the historical control range for untreated TgrasH2 female mice at this age (0 and 0.6% in 100 and 279 mice, respectively). Whilst the No Observable Effect Level (NOEL) for all these tumour incidences was less than the maximum recommended human dose (MRHD), the distribution of these tumour incidences was neither dose-dependent nor statistically significant, and may have been the result of relatively small group sizes exaggerating the proportion of affected animals.

In rats, single incidences of colonic adenoma and caecal adenocarcinoma were observed in different male rats given 1500 mg/kg/day. Whilst the incidence was low and confined to males these tumours are rare in rats (historical controls < 0.1%) and the association with clear dose related mucosal hyperplasia suggested a treatment related effect. However, the low absorption and biliary excretion of aliskiren in rats resulted in high local concentrations in the gastrointestinal tract that were 57-fold higher than human faecal concentrations based on mg/g at the MRHD. Overall, the data suggested that these tumour incidences may not be clinical relevant.

Genotoxicity data for HCTZ

As noted in the International Agency for Research on Cancer (IARC) report on hydrochlorothiazide:

> 'Hydrochlorothiazide did not induce reversion in an *arg*$^-$ strain of *Escherichia coli* (Hs30R) (Fujita, 1985). It was not mutagenic to *Salmonella typhimurium* in the presence or absence of an exogenous metabolic system (Waskell, 1978; Andrews *et al*, 1984) [The Working Group noted that only one concentration was used in both studies.] In strain TA98, but not in TA1535, TA1537 or TA100, a small, reproducible, concentration-dependent increase in the mean number of revertants was observed in the absence, but not in the presence, of an exogenous metabolic system (Mortelmans *et al*, 1986).
>
> In a spot test, hydrochlorothiazide induced nondisjunction and mitotic crossing-over in *Aspergillus nidulans* (Bignami *et al*, 1974).
>
> Hydrochlorothiazide did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* either fed or injected with solutions of 10 mg/mL (Valencia *et al*, 1985).
>
> At concentrations above 500 μg/mL, hydrochlorothiazide produced cytotoxic effects and induced mutations to trifluorothymidine resistance in L5178Y mouse lymphoma cells in the absence of an exogenous metabolic system (National Toxicology Program, 1989). Significant, but not concentration-dependent, increases in the frequency of sister chromatid exchange were observed in Chinese Hamster Ovary (CHO) cells in the presence and absence of an exogenous metabolic system (Galloway *et al*, 1987). Chromosomal aberrations were not found in Chinese Hamster Lung (CHL) cells, but polyploidy was observed after 48 hours treatment (Ishidate, 1988). Chromosomal aberrations were also not detected in CHO cells in the presence or absence of an exogenous metabolic system at concentrations of up to 2600 μg/mL (Galloway et al, 1987).'

Carcinogenicity data for HCTZ

Carcinogenicity studies for HCTZ were conducted in rats and mice (National Toxicological Program, 1989; Bucher *et al*, 1990). There was no evidence for the carcinogenicity of HCTZ in male or female F344/N rats fed doses of 250, 500, or 2,000 ppm (consumed approximately 11, 23, or 89 mg/kg/day, respectively). Equivocal evidence of carcinogenicity for HCTZ was shown in male B6C3F1 mice, based on increased incidences of hepatocellular neoplasms. The incidence of hepatocellular neoplasms was significantly increased in high dose male mice (adenomas, carcinomas, or combined: control, 7/48; low dose, 10/49; high dose, 21/50) but not in female B6C3F1 mice given diets containing 2,500 or 5,000 ppm (consumed approximately 280 or 575 mg/kg/day, respectively) HCTZ. Moreover, the historical incidence of hepatocellular adenomas, carcinomas or combined was also high (30% of the animals) in untreated controls. Taken together, these studies indicate that HCTZ is not carcinogenic in rats and mice up to 534 (for 89 mg/kg/day) and 840 (for 280 mg/kg/day) mg/m^2, respectively, corresponding to exposure ratios greater than 32- and 51-fold the MRHD (25 mg, 0.5 mg/kg, 16.5 mg/m^2) for HCTZ in the aliskiren/HCTZ combination, respectively.

Reproductive and developmental toxicity for HCTZ

In literature provided by the sponsor, HCTZ was shown to penetrate the placental barrier and reach levels in umbilical vein plasma that approach those in maternal plasma. The levels of HCTZ in umbilical cord plasma were 0.1 to 0.8 of that in maternal plasma, and the concentrations of HCTZ in amniotic fluid were up to 5 and 19 times higher than in maternal and umbilical cord plasma, respectively. In a case report where a mother was administered HCTZ (50 mg) routinely, HCTZ was found to be excreted in human milk, but levels of HCTZ were undetectable (limit of quantification [LOQ] 20 ng/mL) in the blood of the breast-fed baby.

More comprehensive information and analysis of the reproductive and developmental toxicity of HCTZ were found in two texts on the use of drugs during pregnancy and lactation. Briggs *et al* (2005) noted that the published experience with first trimester use of thiazides and related diuretics did not indicate that these agents were teratogenic.[4] Diuretics were not recommended for the treatment of gestational hypertension because of the maternal hypovolaemia characteristic of this disease. Other risks to the fetus or newborn included hypoglycaemia, thrombocytopenia, hyponatraemia, hypokalaemia and death from maternal complications. Moreover, thiazide diuretics may have a direct effect on smooth muscle and inhibit labour. An equivalent assessment was provided by Schaefer *et al* (2007)[5].

Nonclinical Summary and Conclusions

Based on the mechanisms of action, the combination of a renin inhibitor (aliskiren) and a thiazide diuretic (HCTZ) is expected to have an additive or synergistic hypotensive effect.

The nonclinical data dossier was limited to a number of analytical methods/validation assays and two repeat dose toxicity studies in rats utilising various doses of combined aliskiren and HCTZ. These combinations were generally in the ratio of 12 to 12.5:1, which was similar to the highest proposed clinical dose combination (300/25 mg).

The toxicity findings in rats at the maximum tolerated dose (MTD) of the combined formulation of aliskiren and HCTZ (150/12 mg/kg) were equivalent to the individual toxicities of aliskiren (150 mg/kg) and HCTZ (12 mg/kg). There were no apparent additive or synergistic effects on toxicity with the combined formulations in this single species. However, the exposure margins based on plasma AUC were less than that expected clinically for aliskiren and 1- to 7-fold for HCTZ. Higher doses led to unacceptable moribundity in rats.

Compared to monotherapy, plasma toxicokinetic analysis in rats indicated that when used as a combined formulation (150/12 mg/kg), HCTZ reduced aliskiren plasma C_{max} and AUC values, whereas aliskiren increased HCTZ plasma C_{max} and AUC values. These findings were consistent for HCTZ but not for aliskiren in a clinical trial utilising the 300/25 mg formulation. The mechanism for this pharmacokinetic interaction was not further addressed by the sponsor.

There were no nonclinical data that explicitly assessed the potential genotoxicity, carcinogenicity or reproductive toxicity of combined aliskiren/HCTZ.

There were no findings in the nonclinical data which would preclude, on safety grounds, the registration of the combination for the treatment of hypertension. This recommendation is consistent with EU guidelines for fixed dose combination products but assumes that there are sufficient clinical safety data which would negate the need for more comprehensive nonclinical data.

IV. Clinical Findings

Introduction

In the clinical development program efficacy and safety data supporting the registration of the fixed combination of aliskiren/HCTZ were assessed in the following studies:

1) a multifactorial design study with adequate doses of each monotherapy component and the combination of the components,

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[4] Chlorothiazide (pp 286-290). In: *Drugs in Pregnancy and Lactation.* 7th edition. Briggs GG, Freeman RK, Yaffe SJ, eds. 2005.Lippincott Williams & Wilkins, Philadelphia, PA, USA.

[5] Schaefer C, Peters P, Miller RK, eds. *Drugs During Pregnancy and Lactation. Treatment options and risk assessment.* 2nd edition. 2007. Academic Press. London UK.

2) studies of the combination therapy in patients who do not adequately respond to aliskiren or HCTZ monotherapy, and

3) a long term (12 months) safety and efficacy study. Overall, the clinical program included nine clinical studies that enrolled a total of 8,472 treated patients. A tabular summary of the clinical trials is provided in Table 1.

Study CSPP100A2204 provides the dose response data. It is also the main study that supports the initial therapy indication, since all patients who were randomised to the aliskiren/HCTZ combination groups in this trial received the combination treatment as the initial therapy without titration from monotherapy.

Study CSPP100A2332 provides pivotal efficacy data to support the use of aliskiren/HCTZ in patients not adequately responding to aliskiren monotherapy.

Study CSPP100A2333 provides pivotal efficacy data and ***Study CSPP100A2331*** and ***Study CSPP100A2309*** provide supportive efficacy data for the use of aliskiren/HCTZ in patients not adequately responding to HCTZ monotherapy.

Study CSPP100A2302 and ***Study CSPP100A2306***, which allowed optional add-on of HCTZ to aliskiren, provide supportive efficacy data for the long term use of the aliskiren/HCTZ combination. ***Study CSPP100A2303***, which was conducted in severe hypertensive patients and allowed optional add-on of HCTZ to aliskiren, provides efficacy data of the aliskiren regimen (including the combination with HCTZ) in the treatment of severe hypertensive patients.

Two studies in which some patients had received treatment with the combination of aliskiren/HCTZ (listed as other clinical studies in Table 3) were also included in the submission; however they were not intended to be used to support the efficacy claims because they included only a small number of patients (total=5) treated with the combination of aliskiren/HCTZ (Japanese Study SPP100A1202); or used a different formulation (Speedel Study CSPP100ACRD07/SPP100 0014).

Study CSPP100A2302 provided data in support of long term efficacy and safety. The study was an open-label, 12 month study that evaluated the long-term combination therapy of aliskiren and HCTZ in the target population. It was primarily a safety study; however efficacy was evaluated as a secondary objective. A 4-month extension to the 12- month study for patients who had already completed at least 8 months of combination therapy with aliskiren/HCTZ 300/25 mg was also conducted: ***Study CSPP100A2302E1***. Study CSPP100A2302 included a 4-week randomised withdrawal period, starting after 11 months of treatment, to evaluate long term efficacy in a subset of patients who were still on aliskiren monotherapy at that time. Since the randomised withdrawal period did not involve patients who had received the combination therapy, the results of the withdrawal period were not discussed in the dossier.

Study CSPP100A2306 was a 26-week study that compared aliskiren to ramipril with the optional addition of HCTZ after 12 weeks of monotherapy to either regimen. This study also included a 4-week placebo-controlled withdrawal and patients on aliskiren/HCTZ were also included in the withdrawal period, therefore, results during the withdrawal period were presented.

All studies were conducted in a multicentre, multi-country setting and in compliance with Good Clinical Practice guidelines.

The application for the registration of aliskiren/HCTZ fixed combination tablets is based on the data from the phase III clinical efficacy/safety studies and bioequivalence studies. Novartis developed the following four doses of aliskiren/HCTZ fixed combination film coated tablets intended for registration − 150/12.5 mg; 150/25 mg; 300/12.5 mg; and 300/25 mg. The pivotal phase III studies supporting the registration of aliskiren/HCTZ for the treatment of hypertension used either the final market image (FMI) formulations of the aliskiren/HCTZ fixed combination or the free combination

of the respective monotherapies. In order to bridge the information obtained with the free combination used in the efficacy and safety studies to the fixed combination FMI film coated tablet products, a bioequivalence development program was conducted as part of the registration application.

Table 3: Overview of studies, their function and other sources of data used

Topic	Source of data
Dose selection studies	None
Short-term placebo-controlled efficacy studies	• **Study CSPP100A2204:** double-blind, placebo-controlled 4 X 4 multifactorial study with aliskiren monotherapy, HCTZ monotherapy and aliskiren in combination with HCTZ
Short-term active-controlled efficacy studies	**Study in patients not adequately responding to aliskiren monotherapy:** • **Study CSPP100A2332:** double-blind, active-controlled study evaluating the combination of aliskiren/HCTZ (300/12.5 mg) and aliskiren/HCTZ (300/25 mg) in non-responders to aliskiren 300 mg **Studies in patients not adequately responding to HCTZ monotherapy:** • **Study CSPP100A2333:** double-blind, active-controlled study evaluating the combination of aliskiren/HCTZ (150/25 mg) and aliskiren/HCTZ (300/25) in non-responders to HCTZ 25 mg • **Study CSPP100A2331:** double-blind, active-controlled study evaluating the combination of aliskiren/valsartan/HCTZ (300/320/25 mg), aliskiren/HCTZ (300/25 mg), and valsartan/HCTZ (320/25 mg) in non-responders to HCTZ 25 mg • **Study CSPP100A2309:** double-blind, active-controlled study evaluating the combination of aliskiren/HCTZ in comparison to HCTZ monotherapy and combination therapies of irbesartan/HCTZ and amlodipine/HCTZ in obese patients non-responders to HCTZ 25 mg **Supportive study:** • **Study CSPP100A2303*:** double-blind, active-controlled study evaluating aliskiren and lisinopril with optional addition of HCTZ in severe hypertension.
Long-term efficacy studies	• **Study CSPP100A2302* / 2302E1:** open-label 12-month study, evaluating aliskiren monotherapy and aliskiren in combination with HCTZ and a 4-month extension to this study • **Study CSPP100A2306*:** double-blind, active-controlled 6-month study comparing aliskiren and ramipril with optional addition of HCTZ
Other clinical studies	• **Study CSPP100A1202*:** open-label 12-month study evaluating aliskiren monotherapy with optional addition of diuretic or CCB in Japanese patients • **Study CRD07/CSPP100A0014*:** open-label, phase II trial of aliskiren monotherapy and aliskiren in combination with HCTZ

*In these studies, open-label addition of HCTZ was permitted or required in patients whose BP was not adequately controlled by other treatment, including aliskiren.

Three definitive bioequivalence (BE) studies were conducted with the dose strengths, 150/25 mg, 300/12.5 mg, and 300/25 mg of aliskiren/HCTZ. Based on the compositional proportionality and similarity in *in vitro* dissolution properties, the sponsor requested a waiver for the dose strength, 150/12.5 mg of aliskiren/HCTZ. The bioequivalence program meets the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency's requirements as per the Australian-adopted *Note for Guidance on the Investigation of Bioavailability and Bioequivalence, CPMP/EWP/QWP/1401/98*.

In this submission, results of the three definitive bioequivalence studies and one food-effect study at the highest dose strength were presented. In addition, the rationale and *in vitro* data supporting the biowaiver are also discussed.

Pharmacokinetics

No new pharmacokinetic data were presented for evaluation. Biopharmaceutical studies were conducted and will be discussed in this section of the evaluation report.

Study CSPH100A2101

A description of this study and the results were discussed in Section II. The clinical evaluator concluded that the FMI tablet containing 150 mg of aliskiren and 25 mg of HCTZ met the bioequivalence criteria relative to the free combination of 150 mg overencapsulated aliskiren and 25 mg HCTZ capsule. The formulations can be considered clinically interchangeable and the efficacy and safety data generated in phase III trials with the free combination of 150 mg of aliskiren and 25 mg HCTZ could be extrapolated to the 150/25 mg aliskiren/HCTZ fixed combination FMI film coated tablet.

Study CSPH100A2102 (Pivotal Bioequivalence, 300/12.5 mg)

A description of this study and the results were discussed in Section II. The clinical evaluator concluded that the rate and extent of absorption of aliskiren and HCTZ were similar following single oral administration of the fixed combination FMI film coated tablet containing 300 mg of aliskiren and 12.5 mg of HCTZ and the free combination of 300 mg aliskiren FMI tablet and 12.5 mg HCTZ capsule. Therefore, the efficacy and safety data generated in phase III trials with the free combination of 300 mg of aliskiren tablet and 12.5 mg HCTZ capsule could be extrapolated to the 300/12.5 mg aliskiren/HCTZ fixed combination FMI tablet.

In the study the intra-subject coefficient of variation (CV%) for aliskiren C_{max} was 60.3%. This high intra-subject variability may have contributed to the marginal failure of aliskiren C_{max} to meet the lower BE boundary of 90% CI.

Although the C_{max} marginally missed BE standards at the low end of the confidence interval, the corresponding geometric mean ratio 0.88 (90% CI = 0.75 - 1.04) indicated similar maximum aliskiren concentrations for the fixed combination tablet and 300 mg aliskiren tablet in the free combination. In addition, the two formulations had the same median time to maximal plasma concentration (t_{max}) value (1 hour), suggesting similar rates of absorption. Overall, the rate and extent of absorption of aliskiren as the fixed combination tablet were similar to the free combination tablet. The lack of strict bioequivalence for aliskiren C_{max} is considered not likely to be clinically significant, as no safety issues would be associated with a reduction in C_{max} and efficacy should not be significantly impacted as there was bioequivalence between aliskiren AUCs.

Study CSPH100A2103 (Pivotal Bioequivalence, 300/25 mg)

A description of this study and the results were discussed in Section II. The clinical evaluator concluded that the FMI tablet containing 300 mg of aliskiren and 25 mg of HCTZ met the bioequivalence criteria relative to the free combination of 300 mg aliskiren FMI tablet and 25 mg HCTZ capsule, therefore the efficacy and safety data generated in phase III trials with the free combination of 300 mg of aliskiren FMI tablet and 25 mg HCTZ could be extrapolated to the 300/25 mg aliskiren/HCTZ fixed combination FMI tablet.

Bio-waiver request for the 150/12.5 mg aliskiren/hydrochlorothiazide dose

The sponsor requested a waiver for the 150/12.5 mg aliskiren/HCTZ fixed combination FMI tablet based on the rationale described below. The rationale is in line with the criteria set in the CHMP's *Note for Guidance on the Investigation of Bioavailability and Bioequivalence, CPMP/EWP/QWP/1401/98*:

- The composition of the 150/12.5 mg aliskiren/HCTZ fixed combination FMI tablet is proportional in its active and inactive ingredients to the 300/25 mg aliskiren/HCTZ fixed combination FMI tablet, for which the bioequivalence was established (Study CSPH100A2103). In addition, the manufacturing process of the two products is similar
- Aliskiren and HCTZ exhibit linear and/or dose proportional pharmacokinetics

- In vitro dissolution of aliskiren and HCTZ three pH media is similar in between the 300/25mg and 150/12.5 mg fixed combination products
- The similar dissolution is further demonstrated by the calculated results of the similarity factors (f2). The f2 is a logarithmic reciprocal square root transformation of the sum of squared errors and is a measurement of the similarity in percent (%) dissolution between the two curves. Similarity factors were obtained using the standard method described in the *Note for Guidance*. According to the CHMP, similarity of the profiles is suggested by f2 similarity factors within a range of 50 and 100.

The evaluator considered that the composition proportionality of the 150/12.5 mg and 300/25 mg aliskiren/HCTZ fixed combination tablets, the similar manufacturing process for these tablets, and the *in vitro* dissolution results adequately fulfil the requirements for waiver of a bioequivalence study at the 150/12.5 mg strength.

Study CSPH100A2104 (Effect of Food)

A description of this study and the results were discussed in Section II. The clinical evaluator concluded that concomitant ingestion of a high-fat meal with aliskiren/HCTZ fixed combination FMI tablet reduced aliskiren exposure and absorption rate. Concomitant ingestion of a high-fat meal with aliskiren/HCTZ fixed combination FMI tablet slightly increased HCTZ exposure.

Overall, study CSPH100A2104 demonstrated that the effect of food on the pharmacokinetics of aliskiren and HCTZ is not different when administered as monotherapy formulation or in aliskiren/HCTZ fixed combination FMI film coated tables. Therefore, it is appropriate to recommend that aliskiren/HCTZ fixed combination FMI film coated tablets be taken with a similar pattern as the one recommended for the respective monotherapy in order to keep consistent pharmacodynamic effects.

Pharmacodynamics

No new pharmacodynamic data were presented for evaluation.

Efficacy

This submission includes studies that had objectives involving the evaluation of the combination therapy of aliskiren/HCTZ or those that had included the treatment of aliskiren in combination with HCTZ. Efficacy was tested in mild to moderate hypertension (90 or 95 to < 110 mmHg diastolic blood pressure [BP]) in most of the studies and in severe hypertension (105-120 mmHg diastolic BP) in only one study. The primary and key secondary efficacy variables were changes in mean sitting diastolic and systolic blood pressure (msDBP and msSBP), and other major secondary variables were response rate and control rate. In addition, certain biomarkers were evaluated: plasma renin activity (PRA) and renin concentration (RC).

The targeted indication for aliskiren/HCTZ combination is the treatment of hypertension. In addition to the application for registration of aliskiren/HCTZ combination in the treatment of hypertensive patients who are not responding to monotherapy, the sponsor is proposing aliskiren/HCTZ combination for use as initial therapy. In relation to the first line indication, the TGA-adopted *Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension CPMP/EWP/238/95 Rev. 2* is relevant. The guideline states that:

The (fixed) combination of two antihypertensive agents in subtherapeutic dose (i.e. dosage lower than the respective lowest approved individual dosage for antihypertensive monotherapy) aims at the reduction of (dose-dependent) adverse drug reactions (taking into account the anticipated increased frequency of idiosyncratic reactions if the patient is simultaneously confronted with two antihypertensive agents new to him).

Furthermore:

At least the following is required if first line therapy is claimed for a fixed low-dose combination:

1. Demonstration that each substance (component) has a documented contribution within the (fixed) combination:

It is necessary (but not sufficient) that the results of a valid clinical trial evaluating a fixed low-dose combination document a statistically significant and clinically relevant greater blood pressure lowering effect (e.g. > 2 mmHg with respect to sitting diastolic blood pressure [sDBP]) than placebo, whereas the difference to each component (same subtherapeutic low dose as in the fixed combination) given separately has to be at least statistically significant. In addition, the response rate on the low-dose fixed combination should exceed that on placebo by an amount which is statistically significant and clinically valuable.

2. Indication for a reduction of (dose-dependent) adverse drug reactions by the low-dose fixed combination as compared to the components in the lowest approved dosages:

It is necessary (but not sufficient) that the blood pressure lowering effect of the low-dose fixed combination is similar, i.e. at least not inferior (e.g. decrease in mean sDBP < 2 mmHg lower than the active comparator) than those of the lowest approved dosage of each component. Moreover, there should be a trend towards better safety and response rate regarding the low-dose fixed combination as compared to each component administered at the lowest approved dosage. Accordingly, the inclusion of a placebo arm in this study is helpful to underline these claims.

The clinical data submitted will therefore need to demonstrate that, at lower doses of the fixed combination, there is benefit in terms of superior efficacy or safety compared to each component used as monotherapy.

All clinical efficacy trials are summarised according to the design or purpose of the trial in Table 3. The sponsor has stated that data and analyses from Study CSPP100A2204 form the main basis to support the initial therapy indication for the fixed combination of aliskiren/HCTZ in the treatment of hypertension, because in this study all patients who were randomised to the aliskiren/HCTZ combination groups received the combination treatment as the initial therapy.

Study CSPP100A2204

Study CSP100A2204 provides the data in relation to dose response assessment as well as the rationale for the selection of aliskiren/HCTZ fixed combination doses for registration for treatment of hypertension. It is nominated as the pivotal study to evaluate the efficacy and safety of the aliskiren/HCTZ combination as initial therapy for the treatment of hypertension in patients with Stage 2 hypertension and patients with additional cardiovascular (CV) risk.

The study enrolled a broad range of hypertensive patients with different degrees of hypertension, and also a range of cardiovascular risk factors such as diabetes, renal impairment, and history of cardiovascular disease. All patients randomised to the combination groups received the combination of aliskiren/HCTZ as initial treatment without titration from monotherapy.

Study CSPP100A2204 was a multifactorial design study with three periods: a washout period, a single-blind, placebo run-in period, and a double-blind treatment period (see Figure 1). During the double-blind treatment period, eligible patients were randomised to one of 15 treatment groups: aliskiren monotherapy 75 mg, 150 mg, or 300 mg once daily (od); HCTZ monotherapy 6.25 mg, 12.5 mg, or 25 mg; the combination of aliskiren/HCTZ 75/6.25 mg, 75/12.5 mg, 75/25 mg, 150/6.25 mg, 150/12.5 mg, 150/25 mg, 300/12.5 mg, or 300/25 mg; or placebo. For patients assigned to receive aliskiren 150 or 300 mg in combination with HCTZ 25 mg, the initial aliskiren/HCTZ dose was 150/12.5 mg for one week. It was then force-titrated to 150/25 mg and 300/25 mg respectively for the rest of the study.

The primary objectives of this study were to:

- Confirm the efficacy of aliskiren 75 mg, 150 mg and 300 mg in patients with essential hypertension by testing the hypothesis of superior reduction in mean sitting systolic blood pressure (msSBP) from Baseline to study end when compared to placebo
- Demonstrate the efficacy of the combination of aliskiren and HCTZ 75/6.25 mg, 75/12.5 mg, 75/25 mg, 150/6.25 mg, 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg in patients with essential hypertension by testing the hypothesis of superior reduction in msDBP from Baseline to study end when compared to the component monotherapies

The secondary objectives of this study were to:

- Confirm the efficacy of aliskiren 75 mg, 150 mg and 300 mg in patients with essential hypertension by testing the hypothesis of superior reduction in msSBP from Baseline to study end when compared to placebo
- Demonstrate the efficacy of the combination of aliskiren and HCTZ 75/6.25 mg, 75/12.5mg, 75/25 mg, 150/6.25 mg, 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg in patients with essential hypertension by testing the hypothesis of superior reduction in msSBP from Baseline to study end when compared to the component monotherapies
- Demonstrate the antihypertensive dose response effect of aliskiren alone and in combination with HCTZ by testing the hypothesis that the magnitude of msDBP and msSBP reduction are related to the dose level of aliskiren and HCTZ administered in this study population
- Assess the proportion of patients achieving a successful response (msDBP < 90 mm Hg or a reduction ≥ 10 mm Hg from Baseline) for all treatment groups
- Explore the safety and tolerability of aliskiren 75 mg, 150 mg and 300 mg, given alone and in combination with HCTZ, in patients with essential hypertension
- Explore the impact of treatment on plasma renin activity (PRA) and plasma rennin concentration (active renin; PRC)

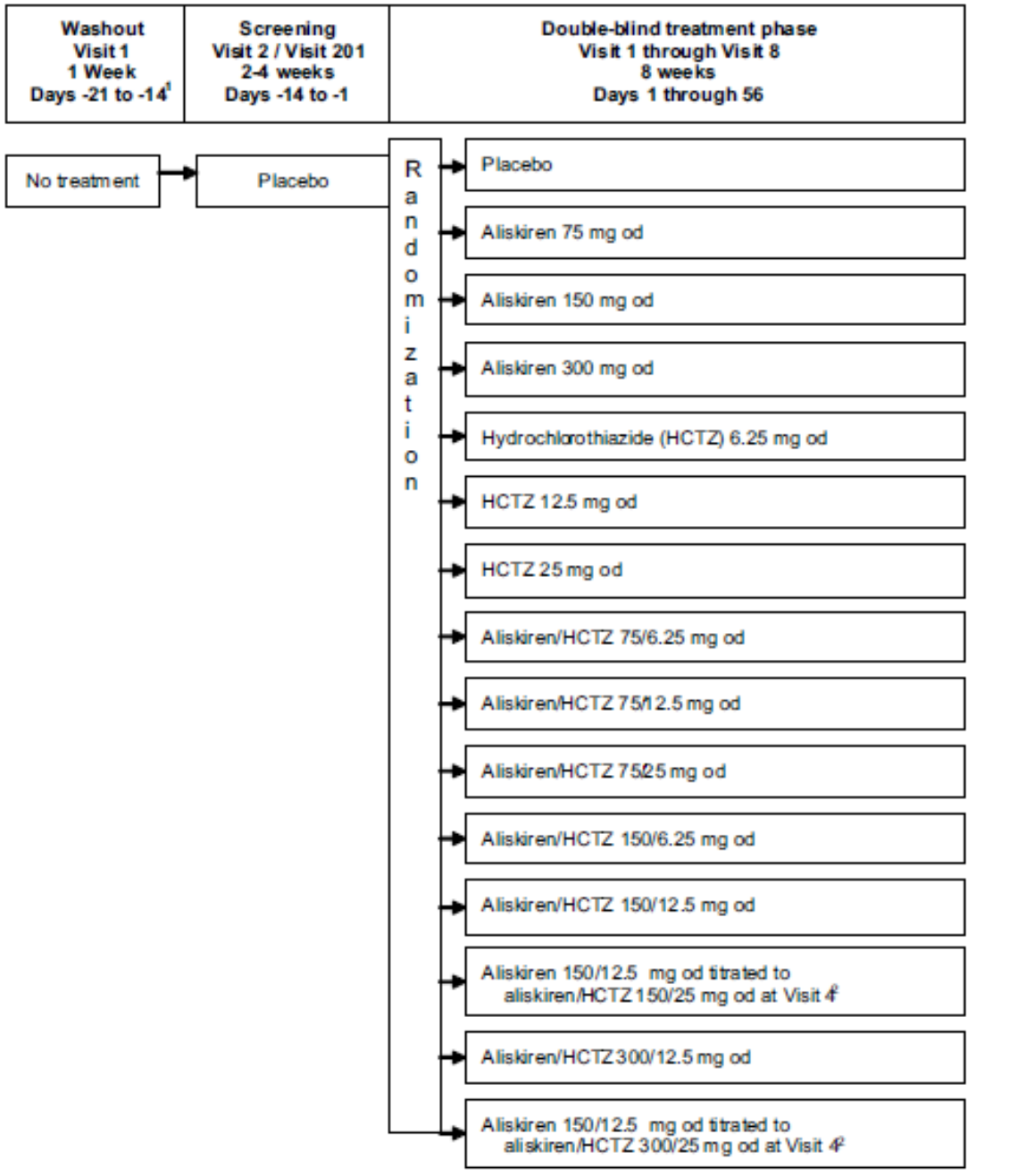
A summary of the key inclusion and exclusion criteria is provided below.

Inclusion criteria

Male or female outpatients, ≥ 18 years of age, with mild-to-moderate essential hypertension, as measured by calibrated standard sphygmomanometer, and defined as:

- msDBP ≥ 90 mm Hg and < 110 mm Hg prior to Visit 3
- msDBP ≥ 95 mm Hg and < 110 mm Hg at Visit 3, and
- an absolute difference of ≤ 10 mm Hg between their average sitting DBP obtained at the randomisation visit and the prior visit (Visits 2 or optional Visit 201).
- Female patients must have been either post-menopausal for one year, surgically sterile, or using effective contraceptive methods such as hormonal or implant contraceptive, barrier method with spermicide, or an intrauterine device.
- Eligible patients were required to provide written informed consent.

Figure 1: Study CSPP100A2204D - Study design



[1] If optional Visit 201 was required to meet randomization criteria, Visits 1, 2, and 201 occurred on Days -35, -28, and -14, respectively.

[2] Forced-titration occurred at Visit 4, which was one week after start of double-blind treatment.

Exclusion criteria

Patients with any of the following conditions were excluded from study participation:

- Pregnant or nursing women
- Any condition that could increase patient risk, prevent study compliance, or jeopardize the evaluation of efficacy or safety, including known or suspected contraindications to the study medications, a history of allergy to thiazide diuretics or to other sulphonamide-derived drugs (a history of allergy to angiotensin receptor blockers was removed as an exclusion criteria; amendment 2)

- Any prior treatment with aliskiren; or participation in an investigational drug study (within one month of Visit 1)
- Severe hypertension (grade 3 WHO classification; msDBP ≥ 110 mm Hg and/or msSBP ≥180 mm Hg)
- History or current evidence of: a secondary form of hypertension; hypertensive encephalopathy or cerebrovascular accident; myocardial infarction, coronary bypass surgery, or any percutaneous coronary intervention (within 12 months); transient ischemic cerebral attack (within 12 months); Keith-Wagener grade III or IV hypertensive retinopathy; malignancy, including leukaemia and lymphoma (within 5 years; but excluding basal cell skin cancer); drug or alcohol abuse (within 12 months); gouty arthritis
- Current diagnosis of: heart failure (New York Heart Association (NYHA) Class II-IV); angina pectoris requiring pharmacological therapy other than sublingual nitroglycerin; second or third degree heart block without a pacemaker; any potentially life-threatening arrhythmia or symptomatic arrhythmia; clinically significant valvular heart disease.
- At Visit 1: Type 1 or Type 2 diabetes mellitus with poor glycaemic control (fasting glycosylated haemoglobin (HbA1c) > 9%); serum sodium and/or potassium less than the lower limit of normal, dehydration, or hyperkalaemia ≥ 5.5 mEq/L; hepatic disease (aspartate transaminase (AST) or alanine transaminase (ALT) values exceeding 2 times the upper limit of normal (2 x ULN), or history of hepatic encephalopathy, oesophageal varices, or portocaval shunt); renal impairment (serum creatinine > 1.5 x ULN), or history of dialysis or nephritic syndrome.
- Any condition that could significantly alter the absorption, distribution, metabolism, or excretion of study drugs including: History of major gastrointestinal tract surgery (gastrectomy, gastroenterostomy, or bowel resection); pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury as indicated by abnormal lipase or amylase; current or previously active inflammatory bowel disease (within 12 months); gastritis, duodenal or gastric ulcers, or gastrointestinal/rectal bleeding (within 3 months).

It is important to note that this study enrolled patients with mild to moderate hypertension; patients with severe hypertension were not eligible. The study can therefore not inform about the efficacy of the aliskiren/HCTZ combination as first line therapy in patients with severe hypertension.

2776 patients were randomised and 2762 were treated. Baseline demographic and background characteristics for all randomised patients indicated that the treatment groups were generally comparable with respect to demographics and baseline characteristics, and reflected the intended target population. The mean age of the randomised population was 54.6 years, while the median age was 55.0 years. Across the treatment groups, 78.9% of patients were younger than 65 years of age, while only 3.6% were 75 years or older. Slightly more than half the patients were male (54.8%) and the vast majority of patients were Caucasian (85.4%).

Approximately 3% of the randomised population was treatment-naive at baseline. Excluding these treatment-naive patients, hypertension was present for a mean of 7.6 years; however, there was a great degree of variability (range of 1.0-51.0 years since diagnosis). Overall, 38.4% of the study patients were obese (body mass index [BMI] ≥ 30 kg / m^2), and metabolic syndrome was present in 35.6% of the randomised population. Approximately 8% of the randomized population had a history of diabetes, and the groups were balanced in this regard.

The following populations were used for the analyses:

Intent-to-Treat (ITT) - All randomised patients who had a Baseline and at least one Post- Baseline efficacy measurement. The treatment in the analyses was the treatment to which the patient was randomised. This is the primary efficacy population.

Per-Protocol (PP) - All ITT patients who completed the study without any major protocol deviations that impact on efficacy assessment. This supplemental efficacy population was used to assess robustness of the primary analysis results. The major protocol deviations were pre-specified prior to unblinding treatment codes for analyses.

Safety (SAF) - All randomised patients who received double-blind trial medication. The treatment in the analyses was the treatment to which the patient was exposed.

Mean exposure was similar in all groups. Rates of safety-related discontinuations were also similar in all groups.

Efficacy results

Efficacy results are presented for the primary efficacy population (ITT), unless otherwise specified (PP population).

Primary efficacy results

The primary efficacy variable was the change from Baseline in mean sitting diastolic blood pressure (msDBP) at Endpoint. A tabular summary of results is provided in Table 4.

Aliskiren monotherapy: Aliskiren monotherapy was more effective than placebo in reducing msDBP at Endpoint ($p = 0.0002$ based on the overall test using Dunnett's multiple comparisons procedure). The least squares mean (LSM) reductions in msDBP at Endpoint for placebo, aliskiren 75, 150, and 300 mg were 6.93, 8.68, 8.94, and 10.26 mm Hg, respectively. Pairwise comparisons found that all 3 doses of aliskiren were statistically superior to placebo based on the nominal p-values. However, the adjusted p-values found that the 150 mg and 300 mg doses were significantly superior to placebo, but the 75 mg dose was not ($p = 0.0890$).

Combination therapy: The overall test showed that both aliskiren and HCTZ had statistically significant contributions to the reductions in msDBP from Baseline at Endpoint ($p < 0.0001$). Most individual combination doses were statistically superior to their component monotherapies (exceptions were: aliskiren/HCTZ 150/6.25 mg to both components; aliskiren/HCTZ 75/12.5 mg to HCTZ 12.5 mg). The LSM reduction in msDBP ranged from 10.76 (aliskiren/HCTZ 75/6.25 mg) to 14.26 (aliskiren/HCTZ 300/25 mg) mm Hg.

Results of a within treatment analysis for changes from Baseline at Endpoint for msDBP demonstrated statistically significant changes within each treatment group ($p < 0.00010$). The active treatment groups had larger mean decreases and larger reductions in msDBP were observed in the higher dose groups and with the combinations.

The results of a within treatment analysis for changes from Baseline at Endpoint for msDBP demonstrated statistically significant changes within each treatment group ($p < 0.0001$). The active treatment groups had larger mean decreases (the smallest change was a decrease of 8.78 mm Hg in the aliskiren 75 mg group; the placebo mean decrease was 7 mm Hg,), and larger reductions in msDBP were observed in the higher dose groups and with the combinations.

Table 4: Study CSPP100A2204 - Statistical analysis of change from Baseline in mean sitting diastolic blood pressure (mm Hg) at Endpoint (ITT population)

Monotherapy	N	LSM change from Baseline (SE)	Combination therapy	N	LSM change from Baseline (SE)
Aliskiren 75 mg	183	-8.68 (0.59)	Aliskiren 75 mg/HCTZ 6.25 mg	187	-10.76 (0.59)
Aliskiren 150 mg	183	-8.94 (0.59)	Aliskiren 75 mg/HCTZ 12.5 mg	189	-11.14 (0.59)
Aliskiren 300 mg	180	-10.26 (0.60)	Aliskiren 75 mg/HCTZ 25 mg	186	-11.46 (0.59)
HCTZ 6.25 mg	194	-9.07 (0.58)	Aliskiren 150 mg/HCTZ 6.25 mg	173	-10.36 (0.61)
HCTZ 12.5 mg	188	-10.11 (0.59)	Aliskiren 150 mg/HCTZ 12.5 mg	184	-11.90 (0.59)
HCTZ 25 mg	173	-9.37 (0.61)	Aliskiren 150 mg/HCTZ 25 mg	187	-12.65 (0.59)
Placebo	192	-6.93 (0.58)	Aliskiren 300 mg/HCTZ 12.5 mg	180	-13.87 (0.60)
			Aliskiren 300 mg/HCTZ 25 mg	173	-14.26 (0.61)

Pairwise Comparison		LSM difference: Change from Baseline (SE)	LSM difference: 95% CI	Nominal p-value
Aliskiren 75 mg	vs. placebo	-1.75 (0.83)	(-3.37, -0.13)	0.0344*
Aliskiren 150 mg	vs. placebo	-2.01 (0.83)	(-3.63, -0.39)	0.0152*
Aliskiren 300 mg	vs. placebo	-3.33 (0.83)	(-4.95, -1.70)	< 0.0001*
Aliskiren 75 mg/HCTZ 6.25 mg	vs. aliskiren 75 mg	-2.08 (0.83)	(-3.71, -0.45)	0.0126*
	vs. HCTZ 6.25 mg	-1.69 (0.82)	(-3.30, -0.08)	0.0394*
	vs. placebo	-3.83 (0.82)	(-5.44, -2.22)	< 0.0001*
Aliskiren 75 mg/HCTZ 12.5 mg	vs. aliskiren 75 mg	-2.46 (0.83)	(-4.09, -0.83)	0.0031*
	vs. HCTZ 12.5 mg	-1.03 (0.83)	(-2.65, 0.59)	0.2124
	vs. placebo	-4.21 (0.82)	(-5.82, -2.60)	< 0.0001*
Aliskiren 75 mg/HCTZ 25 mg	vs. aliskiren 75 mg	-2.77 (0.83)	(-4.41, -1.14)	0.0009*
	vs. HCTZ 25 mg	-2.09 (0.85)	(-3.75, -0.43)	0.0136*
	vs. placebo	-4.52 (0.82)	(-6.14, -2.91)	< 0.0001*
Aliskiren 150 mg/HCTZ 6.25 mg	vs. aliskiren 150 mg	-1.41 (0.85)	(-3.08, 0.25)	0.0962
	vs. HCTZ 6.25 mg	-1.29 (0.84)	(-2.93, 0.36)	0.1249
	vs. placebo	-3.42 (0.84)	(-5.07, -1.78)	< 0.0001*
Aliskiren 150 mg/HCTZ 12.5 mg	vs. aliskiren 150 mg	-2.96 (0.84)	(-4.60, -1.32)	0.0004*
	vs. HCTZ 12.5 mg	1.79 (0.83)	(-3.42, -0.16)	0.0314*
	vs. placebo	-4.97 (0.83)	(-6.59, -3.35)	< 0.0001*
Aliskiren 150 mg/HCTZ 25 mg	vs. aliskiren 150 mg	-3.70 (0.83)	(-5.33, -2.07)	< 0.0001*
	vs. HCTZ 25 mg	-3.28 (0.85)	(-4.94, -1.62)	0.0001*
	vs. placebo	-5.71 (0.82)	(-7.33, -4.10)	< 0.0001*
Aliskiren 300 mg/HCTZ 12.5 mg	vs. aliskiren 300 mg	-3.61 (0.84)	(-5.26, -1.95)	< 0.0001*
	vs. HCTZ 12.5 mg	-3.76 (0.84)	(-5.39, -2.12)	< 0.0001*
	vs. placebo	-6.93 (0.83)	(-8.56, -5.31)	< 0.0001*
Aliskiren 300 mg/HCTZ 25 mg	vs. aliskiren 300 mg	-4.00 (0.85)	(-5.68, -2.33)	< 0.0001*
	vs. HCTZ 25 mg	-4.90 (0.86)	(-6.59, -3.21)	< 0.0001*
	vs. placebo	-7.33 (0.84)	(-8.98, -5.68)	< 0.0001*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval

* indicates statistical significance at the 0.05 level.

Dunnett's procedure between aliskiren monotherapy and placebo: statistical significance between placebo and at least one aliskiren treatment; smallest Dunnett's adjusted p-value was 0.0002.

Secondary efficacy parameters

The results for the main secondary efficacy assessment, the changes in mean systolic blood pressure (msSBP), were generally similar to those for msDBP (see Table 5).

Table 5: Study CSPP100A2204 - Statistical analysis of mean change from Baseline in mean sitting systolic blood pressure (mm Hg) at Endpoint (ITT population)

Monotherapy	N	LSM change from Baseline (SE)	Combination therapy	N	LSM change from Baseline (SE)
Aliskiren 75 mg	183	-9.37 (0.94)	Aliskiren 75 mg/HCTZ 6.25 mg	187	-14.29 (0.93)
Aliskiren 150 mg	183	-12.24 (0.94)	Aliskiren 75 mg/HCTZ 12.5 mg	189	-15.64 (0.93)
Aliskiren 300 mg	180	-15.74 (0.95)	Aliskiren 75 mg/HCTZ 25 mg	186	-17.32 (0.93)
HCTZ 6.25 mg	194	-10.95 (0.92)	Aliskiren 150 mg/HCTZ 6.25 mg	173	-15.31 (0.97)
HCTZ 12.5 mg	188	-13.92 (0.93)	Aliskiren 150 mg/HCTZ 12.5 mg	184	-17.61 (0.94)
HCTZ 25 mg	173	-14.30 (0.97)	Aliskiren 150 mg/HCTZ 25 mg	187	-19.47 (0.93)
Placebo	192	-7.48 (0.92)	Aliskiren 300 mg/HCTZ 12.5 mg	180	-19.82 (0.95)
			Aliskiren 300 mg/HCTZ 25 mg	173	-21.22 (0.97)

Pairwise Comparison		LSM difference		
		Change from Baseline (SE)	95% CI	Nominal p-value
Aliskiren 75 mg	vs. placebo	-1.89 (1.31)	(-4.46, 0.69)	0.1512
Aliskiren 150 mg	vs. placebo	-4.76 (1.31)	(-7.34, -2.18)	0.0003*
Aliskiren 300 mg	vs. placebo	-8.25 (1.32)	(-10.84, -5.67)	< 0.0001*
Aliskiren 75 mg/HCTZ 6.25 mg	vs. aliskiren 75 mg	-4.93 (1.32)	(-7.52, -2.33)	0.0002*
	vs. HCTZ 6.25 mg	-3.34 (1.30)	(-5.90, -0.79)	0.0103*
	vs. placebo	-6.81 (1.31)	(-9.38, -4.25)	< 0.0001*
Aliskiren 75 mg/HCTZ 12.5 mg	vs. aliskiren 75 mg	-6.27 (1.32)	(-8.86, -3.69)	< 0.0001*
	vs. HCTZ 12.5 mg	-1.71 (1.31)	(-4.28, 0.85)	0.1905
	vs. placebo	-8.16 (1.30)	(-10.71, -5.60)	< 0.0001*
Aliskiren 75 mg/HCTZ 25 mg	vs. aliskiren 75 mg	-7.95 (1.32)	(-10.55, -5.36)	< 0.0001*
	vs. HCTZ 25 mg	-3.02 (1.34)	(-5.66, -0.39)	0.0246*
	vs. placebo	-9.84 (1.31)	(-12.40, -7.27)	< 0.0001*
Aliskiren 150 mg/HCTZ 6.25 mg	vs. aliskiren 150 mg	-3.07 (1.35)	(-5.71, -0.42)	0.0230*
	vs. HCTZ 6.25 mg	-4.36 (1.33)	(-6.97, -1.75)	0.0011*
	vs. placebo	-7.83 (1.33)	(-10.44, -5.21)	< 0.0001*
Aliskiren 150 mg/HCTZ 12.5 mg	vs. aliskiren 150 mg	-5.37 (1.33)	(-7.97, -2.77)	< 0.0001*
	vs. HCTZ 12.5 mg	-3.69 (1.32)	(-6.27, -1.10)	0.0052*
	vs. placebo	-10.13 (1.31)	(-12.70, -7.56)	< 0.0001*
Aliskiren 150 mg/HCTZ 25 mg	vs. aliskiren 150 mg	-7.23 (1.32)	(-9.82, -4.64)	< 0.0001*
	vs. HCTZ 25 mg	-5.17 (1.34)	(-7.81, -2.54)	0.0001*
	vs. placebo	-11.99 (1.31)	(-14.55, -9.43)	< 0.0001*
Aliskiren 300 mg/HCTZ 12.5 mg	vs. aliskiren 300 mg	-4.08 (1.34)	(-6.71, -1.45)	0.0024*
	vs. HCTZ 12.5 mg	-5.89 (1.33)	(-8.49, -3.29)	< 0.0001*
	vs. placebo	-12.33 (1.32)	(-14.92, -9.75)	< 0.0001*
Aliskiren 300 mg/HCTZ 25 mg	vs. aliskiren 300 mg	-5.48 (1.35)	(-8.14, -2.83)	< 0.0001*
	vs. HCTZ 25 mg	-6.92 (1.37)	(-9.60, -4.24)	< 0.0001*
	vs. placebo	-13.74 (1.33)	(-16.35, -11.1)	< 0.0001*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval

* indicates statistical significance at the 0.05 level.

Dunnett's procedure between aliskiren monotherapy and placebo: statistical significance between placebo and at least one aliskiren treatment; the smallest Dunnett's adjusted p-value was < 0.0001.

Aliskiren monotherapy: Aliskiren monotherapy was more effective than placebo in reducing msSBP at Endpoint ($p < 0.0001$). The LSM reductions in msSBP at Endpoint for placebo, aliskiren 75, 150, and 300 mg were 7.48, 9.37, 12.24, and 15.74 mm Hg, respectively. Consistent results were obtained from both the nominal p-values (pairwise comparisons) and the adjusted p-values using the Dunnett's multiple comparisons procedure: both found that the 150 and 300 mg doses were significantly superior to placebo and that the 75 mg dose was not.

Combination therapy: The overall test showed that both aliskiren and HCTZ had statistically significant contributions to the reductions in msSBP from Baseline at Endpoint ($p < 0.0001$). Most combination doses were statistically superior to their component monotherapies (exception:

aliskiren/HCTZ 75/12.5 mg to HCTZ 12.5 mg). The LSM reduction in msSBP ranged from 14.29 (aliskiren/HCTZ 75/6.25 mg) to 21.22 (aliskiren/HCTZ 300/25 mg).

Responder rate analysis

The between-treatment comparisons of responder rates (msDBP < 90 mm Hg and/or ≥ 10 mm Hg decrease from Baseline) showed that aliskiren 300 mg and all combination therapy doses were significantly superior to placebo. Further, combinations of the two lower doses of aliskiren (75 and 150 mg) with HCTZ 25 mg and the highest dose of aliskiren (300 mg) with HCTZ (12.5 and 25 mg) were significantly superior to their component monotherapies. Combinations of aliskiren (75 and 150 mg) with HCTZ 12.5 mg were significantly superior to the respective aliskiren doses (see Table 6).

It should be noted that the aliskiren/HCTZ 150/12.5 mg dose was not superior to HCTZ 12.5 mg alone.

Table 6: Study CSPP100A2204 -Number (%) of responders in mean sitting diastolic blood pressure (mm Hg) at Endpoint by treatment group (ITT population)

Pairwise Comparison		Treatment A		Treatment B		p-value
A	vs. B	n/N	(%)	n/N	(%)	
Aliskiren 75 mg	vs. placebo	95/183	51.9	88/192	45.8	0.2181
Aliskiren 150 mg	vs. placebo	95/183	51.9	88/192	45.8	0.3728
Aliskiren 300 mg	vs. placebo	115/180	63.9	88/192	45.8	0.0005*
Aliskiren 75 mg/HCTZ 6.25 mg	vs. aliskiren 75 mg	115/187	61.5	95/183	51.9	0.0902
	vs. HCTZ 6.25 mg			104/194	53.6	0.1459
	vs. placebo			88/192	45.8	0.0033*
Aliskiren 75 mg/HCTZ 12.5 mg	vs. aliskiren 75 mg	120/189	63.5	95/183	51.9	0.0118*
	vs. HCTZ 12.5 mg			114/188	60.6	0.3660
	vs. placebo			88/192	45.8	0.0002*
Aliskiren 75 mg/HCTZ 25 mg	vs. aliskiren 75 mg	131/186	70.4	95/183	51.9	0.0005*
	vs. HCTZ 25 mg			102/173	59.0	0.0284*
	vs. placebo			88/192	45.8	< 0.0001*
Aliskiren 150 mg/HCTZ 6.25 mg	vs. aliskiren 150 mg	101/173	58.4	95/183	51.9	0.1566
	vs. HCTZ 6.25 mg			104/194	53.6	0.4013
	vs. placebo			88/192	45.8	0.0214*
Aliskiren 150 mg/HCTZ 12.5 mg	vs. aliskiren 150 mg	128/184	69.6	95/183	51.9	0.0002*
	vs. HCTZ 12.5 mg			114/188	60.6	0.0690
	vs. placebo			88/192	45.8	< 0.0001*
Aliskiren 150 mg/HCTZ 25 mg	vs. aliskiren 150 mg	133/187	71.1	95/183	51.9	0.0002*
	vs. HCTZ 25 mg			102/173	59.0	0.0302*
	vs. placebo			88/192	45.8	< 0.0001*
Aliskiren 300 mg/HCTZ 12.5 mg	vs. aliskiren 300 mg	145/180	80.6	115/180	63.9	0.0002*
	vs. HCTZ 12.5 mg			114/188	60.6	< 0.0001*
	vs. placebo			88/192	45.8	< 0.0001*
Aliskiren 300 mg/HCTZ 25 mg	vs. aliskiren 300 mg	133/173	76.9	115/180	63.9	0.0058*
	vs. HCTZ 25 mg			102/173	59.0	0.0003*
	vs. placebo			88/192	45.8	< 0.0001*

Responder: a patient with trough msDBP < 90 mm Hg and/or ≥ 10 mm Hg reduction from Baseline (Week 0).
p-values were from a logistic regression model with treatment and region as factors and Baseline as a covariate.
N = Number of patients with Baseline and Endpoint msDBP values.
* indicates statistical significance at 0.05 level.

Control rates in Study CSPP100A2204

Control rates (percentages of patients with BP control, defined as having msSBP < 140mmHg and msDBP < 90 mmHg) in Study CSPP100A2204 are summarised in Table 7. For the proportion of patients achieving BP control, significant superiority to component monotherapies was observed in all combinations of aliskiren 150 mg or 300 mg with HCTZ 12.5 mg or 25 mg.

Table 7: Study CSPP100A2204 - Number (%) of patients achieving BP control at endpoint (primary ITT population)

Pairwise Comparisons		Treatment A		Treatment B		
A	vs. .B	n/N	%	n/N	%	p-value
Aliskiren 75 mg	vs. placebo	53/183	29.0	54/192	28.1	0.7529
Aliskiren 150 mg	vs. placebo	70/183	38.3	54/192	28.1	0.0700
Aliskiren 300 mg	vs. placebo	84/180	46.7	54/192	28.1	0.0001*
Aliskiren 75 mg/HCTZ 6.25 mg	vs. aliskiren 75 mg	70/187	37.4	53/183	29.0	0.1431
	vs. HCTZ 6.25 mg			63/194	32.5	0.4206
	vs. placebo			54/192	28.1	0.0718
Aliskiren 75 mg/HCTZ 12.5 mg	vs. aliskiren 75 mg	81/189	42.9	53/183	29.0	0.0012*
	vs. HCTZ 12.5 mg			71/188	37.8	0.0897
	vs. placebo			54/192	28.1	0.0003*
Aliskiren 75 mg/HCTZ 25 mg	vs. aliskiren 75 mg	92/186	49.5	53/183	29.0	0.0002*
	vs. HCTZ 25 mg			64/173	37.0	0.0253*
	vs. placebo			54/192	28.1	<.0001*
Aliskiren 150 mg/HCTZ 6.25 mg	vs. aliskiren 150 mg	71/173	41.0	70/183	38.3	0.4221
	vs. HCTZ 6.25 mg			63/194	32.5	0.1089
	vs. placebo			54/192	28.1	0.0103*
Aliskiren 150 mg/HCTZ 12.5 mg	vs. aliskiren 150 mg	91/184	49.5	70/183	38.3	0.0114*
	vs. HCTZ 12.5 mg			71/188	37.8	0.0163*
	vs. placebo			54/192	28.1	<.0001*
Aliskiren 150 mg/HCTZ 25 mg	vs. aliskiren 150 mg	101/187	54.0	70/183	38.3	0.0028*
	vs. HCTZ 25 mg			64/173	37.0	0.0047*
	vs. placebo			54/192	28.1	<.0001*
Aliskiren 300 mg/HCTZ 12.5 mg	vs. aliskiren 300 mg	107/180	59.4	84/180	46.7	0.0057*
	vs. HCTZ 12.5 mg			71/188	37.8	<.0001*
	vs. placebo			54/192	28.1	<.0001*
Aliskiren 300 mg/HCTZ 25 mg	vs. aliskiren 300 mg	103/173	59.5	84/180	46.7	0.0094*
	vs. HCTZ 25 mg			64/173	37.0	<.0001*
	vs. placebo			54/192	28.1	<.0001*

A patient with control in BP was defined as having a msDBP <90 mmHg and a msSBP <140 mmHg.

The control rate was analyzed by using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.

* Indicates statistical significance at 0.05 level.

Plasma renin activity (PRA) and renin concentration (RC)

In Study CSPP100A2204, treatment with all three aliskiren monotherapy doses was also associated with reductions in PRA (54%, 65%, and 58% for the 75 mg, 150 mg, and 300 mg dose groups, respectively). Despite the expected increases in PRA found with HCTZ monotherapy, all of the combination dose groups had PRA reductions, ranging from 46% in the aliskiren/HCTZ 150/25 group to 63% in the aliskiren/HCTZ 50/6.25 group.

Greater increases in RC with increasing doses were found for the aliskiren and HCTZ monotherapy treatment groups, and the increases were greater with aliskiren than with HCTZ. The greatest mean increases were observed in the combination dose groups.

Overall, these results were consistent with the known pharmacology of many antihypertensives, which lead to a compensatory rise in renin release from the juxtaglomerular cells of the kidney through its inhibition of the active enzyme. When used in combination with HCTZ, aliskiren blocks the reactive rise in PRA that would otherwise occur with HCTZ monotherapy.

Analyses relevant to the initial therapy indication for aliskiren/HCTZ combination

The sponsor performed post hoc analyses that were intended to support the initial therapy indication. These additional efficacy analyses were performed exclusively for Study CSPP100A2204, which was the only study in which all patients randomised to the combination groups received the combination of aliskiren/HCTZ as the initial treatment without titration from monotherapy.

Two special subgroups were formed post hoc for the purpose of analyses to support the initial therapy indication of aliskiren/HCTZ combination: patients with markedly elevated blood pressure (Stage 2 hypertension) and patients with additional CV risk.

Stage 2 hypertension is defined as either baseline msSBP ≥160 mmHg or msDBP ≥100 mmHg. Patients with additional CV risk were identified as those with any one of the following: diabetes, renal impairment/decreased glomerular filtration rate (GFR) (<90 ml/min/1.73 m^2 at the study baseline), or history of CV diseases, regardless of the baseline blood pressure level. The numbers of patients based on hypertension stage and additional CV risk are shown in Table 8.

Table 8: Study CSPP100A2204 - Number (%) of patients by hypertension stage and additional CV risk - Group A (short-term placebo-controlled study) (ITT population)

	Placebo N=192	Mono Ali N=546	Mono HCTZ N=555	Ali/HCTZ 150/12.5 mg N=184	Ali/HCTZ 150/25 mg N=187	Ali/HCTZ 300/12.5 mg N=180	Ali/HCTZ 300/25 mg N=173	Ali/HCTZ N=1459
Hypertension Stage 2	100 (52.1%)	296 (54.2)	302 (54.4%)	100 (54.3%)	93 (49.7%)	96 (53.3%)	94 (54.3%)	773 (53.0%)
Additional CV Risk = yes*	132 (68.8%)	351 (64.3%)	360 (64.9%)	107 (58.2%)	122 (65.2%)	123 (68.3%)	127 (73.4%)	960 (65.8%)

* percents were calculated from data in source tables

The analyses from Study CSPP100A2204 confirmed that all aliskiren/HCTZ combination doses proposed for registration (150/12.5mg, 150/25mg, 300/12.5mg, and 300/25mg) when used as the initial therapy demonstrated statistically greater msDBP and msSBP reductions than the respective monotherapies in patients with Stage 2 hypertension. The greatest reductions were seen with aliskiren/HCTZ 300/25 mg. Tabular summaries of results are shown in Tables 9 and 10.

Table 9: Study CSPP100A2204 - Placebo-subtracted LS Mean Reduction in msDBP (mmHg) at Endpoint in Stage 2 hypertensive patients (ITT population)

	Placebo	Aliskiren 150 mg	Aliskiren 300 mg
Placebo	—	-1.72	-2.92 [a]
HCTZ 12.5 mg	-2.51 [a]	-5.99 [a, b, c]	-7.75 [a, b, c]
HCTZ 25 mg	-3.50 [a]	-6.85 [a, b, c]	-8.06 [a, b, c]

Placebo response: -6.39 mmHg
[a] Statistically significant difference vs. placebo (p <0.05)
[b] Statistically significant difference vs. aliskiren component (p <0.05)
[c] Statistically significant difference vs. HCTZ component (p <0.05)

Table 10: Study CSPP100A2204 - Placebo-subtracted LS Mean reduction in msSBP (mmHg) at Endpoint in Stage 2 hypertensive patients (ITT population)

	Placebo	Aliskiren 150 mg	Aliskiren 300 mg
Placebo	—	-4.55 [a]	-8.59 [a]
HCTZ 12.5 mg	-6.89 [a]	-11.84 [a, b, c]	-13.38 [a, b, c]
HCTZ 25 mg	-8.01 [a]	-13.00 [a, b, c]	-16.06 [a, b, c]

Placebo response: -8.71 mmHg

[a] Statistically significant difference vs. placebo (p <0.05)
[b] Statistically significant difference vs. aliskiren component (p <0.05)
[c] Statistically significant difference vs. HCTZ component (p <0.05)

Table 11 summarises control rates (percentages of patients with BP control, defined as having msSBP < 140 mmHg and msDBP < 90 mmHg) from Study CSPP100A2204 in Stage 2 hypertensive patients treated with the four doses of aliskiren/HCTZ combination proposed for registration. Significant superiority to each of the component monotherapies in BP control rate was observed at these four doses.

Supplemental analyses for individual SBP control (<140 mmHg) rate and individual DBP control (<90 mmHg) showed that overall a greater number of patients achieved BP control over respective monotherapies by these definitions. A notable exception was the aliskiren/HCTZ 150/25 mg dose which was not superior to HCTZ 25 mg alone (p =0.0956).

Table 11: Study CSPP100A2204 - Percent of patients achieving BP control (msSBP/ msDBP < 140/90 mmHg) at endpoint in Stage 2 hypertensive patients (ITT population)

	Placebo	Aliskiren 150 mg	Aliskiren 300 mg
Placebo	17.0%	26.0%	32.0% [a]
HCTZ 12.5 mg	22.5%	38% [a, b, c]	47.9% [a, b, c]
HCTZ 25 mg	25.8%	43% [a, b, c]	47.9% [a, b, c]

[a] statistically significant difference vs. placebo (p <0.05)
[b] statistically significant difference vs. aliskiren component (p <0.05)
[c] statistically significant difference vs. HCTZ component (p <0.05)

Since patients with additional CV risk require more aggressive BP control, a sub- analysis using a BP control goal of <130/80 mmHg was performed in Stage 2 patients who also had additional CV risk. Several of the results did not establish that combination therapy with aliskiren/HCTZ was statistically significantly superior to monotherapy. In particular:

- aliskiren/HCTZ 150/12.5 mg was not superior to aliskiren 150 mg alone
- aliskiren/HCTZ 150/25 mg was not superior to aliskiren 150 mg alone
- aliskiren/HCTZ 300/12.5 mg was not superior to aliskiren 300 mg alone
- aliskiren/HCTZ 300/12.5 mg was not superior to HCTZ 12.5 mg alone
- aliskiren/HCTZ 300/12.5 mg was not superior to placebo
- aliskiren/HCTZ 300/25 mg was not superior to aliskiren 300 mg alone.
-

The evaluator noted that the results in relation to use of combination therapy in patients with additional cardiovascular risk do not support that combination therapy should be used first line.

Supplemental statistical analyses were performed post-hoc for msSBP and msDBP reduction and overall blood pressure control (msSBP <130 mmHg and msDBP <80 mmHg) in patients with additional CV risks. The identification of patients with additional CV risk was based on the patient's prior medical history and baseline GFR. The conditions defined as CV risk included the following: diabetes, renal impairment (GFR <90 ml/min/1.73 m^2) and history of relevant CV disease.

Tables 12 and 13 summarise the placebo-subtracted LS Mean reduction in msDBP and msSBP (mmHg) with all doses of aliskiren/HCTZ combination proposed for registration and their

respective monotherapies in patients with additional CV risk. The between-treatment analysis showed that several of the combination doses demonstrated statistically greater msDBP and msSBP reductions than either of their component monotherapies. The exception in these analyses was msDBP and msSBP reductions with aliskiren150mg/HCTZ 12.5mg combination that were statistically significantly greater than aliskiren 150 mg but not statistically significantly greater than HCTZ 12.5mg.

Table 12: Study CSPP100A2204 - Placebo-subtracted LS Mean Reduction in msDBP (mmHg) at endpoint in patients with additional CV risk (ITT population)

	Placebo	Aliskiren 150 mg	Aliskiren 300 mg
Placebo	--	-1.08	-3.03 [a]
HCTZ 12.5 mg	-2.47 [a]	-3.93 [a, b]	-5.92 [a, b, c]
HCTZ 25 mg	-2.72 [a]	-4.95 [a, b, c]	-7.34 [a, b, c]

Placebo response: -7.35 mmHg
[a] Statistically significant difference vs. placebo (p <0.05)
[b] Statistically significant difference vs. aliskiren component (p <0.05)
[c] Statistically significant difference vs. HCTZ component (p <0.05)

Table 13: Study CSPP100A2204 Placebo-subtracted LS Mean Reduction in msSBP (mmHg) at endpoint in patients with additional CV risk (ITT population)

	Placebo	Aliskiren 150 mg	Aliskiren 300 mg
Placebo	--	-3.95[a]	-6.52[a]
HCTZ 12.5 mg	-6.34 [a]	-8.88[a,b]	-11.20[a,b,c]
HCTZ 25 mg	-7.20 [a]	-12.20 [a,b,c]	-13.60[a,b,c]

Placebo response: -8.15 mmHg
[a] Statistically significant difference vs. placebo (p <0.05)
[b] Statistically significant difference vs. aliskiren component (p <0.05)
[c] Statistically significant difference vs. HCTZ component (p <0.05)

In patients who had additional CV risks, the percent of patients achieving more aggressive BP control (msSBP <130 mmHg and msDBP <80 mmHg) was assessed, and the results for the proposed doses of aliskiren/HCTZ combination and their respective monotherapies are summarised in Table 14. For msDBP the combinations of aliskiren/HCTZ 150/12.5mg and 300/12.5mg demonstrated significant superiority over aliskiren monotherapy, but not HCTZ monotherapy. The combinations of aliskiren/HCTZ 150/25mg and 300/25mg demonstrated significant superiority to both component monotherapies.

Table 14: Study CSPP100A2204 - Percent of patients achieving more aggressive BP control (msSBP/ msDBP less than 130/80 mmHg) at endpoint in patients with additional CV risk (ITT population)

	Placebo	Aliskiren 150 mg	Aliskiren 300 mg
Placebo	1.5%	3.4%	4.3%
HCTZ 12.5 mg	10.2% [a]	11.2% [a, b]	13.8% [a, b]
HCTZ 25 mg	6.1%	19.8% [a, b, c]	21.3% [a, b, c]

[a] statistically significant difference vs. placebo (p <0.05)
[b] statistically significant difference vs. aliskiren component (p <0.05)
[c] statistically significant difference vs. HCTZ component (p <0.05)

When the msSBP control <130 mmHg rate was assessed in patients with additional CV risk, all aliskiren/HCTZ combination doses proposed for registration demonstrated statistically significantly greater control rate than each of the respective monotherapies with the exception of the 150/25mg dose in which the comparison to HCTZ 25mg did not reach statistical significance (P=0.081) (see Table 15). Individual msDBP control (<80 mmHg) rates were assessed, and the results showed a similar trend to the overall control (<130/80 mmHg) rate.

Table 15: Study CSPP100A2204 - Percent of patients achieving more aggressive SBP control (msSBP less than 130 mmHg) at endpoint in patients with additional CV risk (ITT population)

	Placebo	Aliskiren 150 mg	Aliskiren 300 mg
Placebo	9.9%	21.1%[a]	28.1%[a]
HCTZ 12.5 mg	25.2%[a]	36.8%[a,b,c]	41.2%[a,b,c]
HCTZ 25 mg	22.1%[a]	33.3%[a,b]	40.2%[a,b,c]

[a] statistically significant difference vs. placebo ($p < 0.05$)
[b] statistically significant difference vs. aliskiren component ($p < 0.05$)
[c] statistically significant difference vs. HCTZ component ($p < 0.05$)

The evaluator noted that these results above do not support use of the of aliskiren/HCTZ 150/12.5mg and 300/12.5mg combination over HCTZ monotherapy alone, and do not support first line use of the combination. The aliskiren/HCTZ 150/25 mg combination was also not shown to be superior to 25 mg of HCTZ alone.

Subgroup analyses

Subgroups of age, gender, race, ethnicity, and obesity status were examined for their efficacy response and dosing needs. Summary statistics of the change from baseline to endpoint for msDBP, msDBP, control rate, and response rate were produced by treatment group for each of the demographic subgroups. No clinically significant differences were observed in the subgroup analyses compared to the overall population.

Study CSPP100A 2332

Study CSPP100A 2332 provided efficacy data to evaluate the use of aliskiren/HCTZ combination in patients with blood pressure not adequately responding to aliskiren monotherapy. The efficacy data are relevant to assessment of the aliskiren/HCTZ combination as second line therapy.

This was an eight-week, randomised, double-blind, parallel-group, multicentre study with three treatment groups: aliskiren 300 mg, aliskiren/HCTZ 300/25 mg, and aliskiren/HCTZ 300/12.5 mg. The study had three periods: a 4 day washout, a 4 week single-blind run-in with aliskiren 300 mg and an 8 week double- blind treatment. The primary efficacy variable was change from baseline (Visit 4) in msDBP at endpoint.

Patient characteristics were comparable across the three treatment groups. In all groups the number of females participating was slightly lower than the number of males. The age-group distribution was similar in the three treatment groups, with a total of 80.8% of the patients being younger than 65 years of age. Mean duration of hypertension was approximately 8 years in all treatment groups. Patients in all groups had an average body weight of approximately 81 kg. Mean BMI was approximately 29 kg/m^2 in all groups. Slightly more than one third of the patient population (37.6%) was obese (BMI $\geq$ 30 kg/m^2). Baseline blood pressure values were comparable in the three treatment groups. Mean exposure was similar in all groups. Rates of safety-related discontinuations were also similar in all groups.

Efficacy Results

msDBP and msSBP

In this study with patients not adequately responsive to aliskiren monotherapy, both aliskiren/HCTZ 300/25 mg and aliskiren/HCTZ 300/12.5 mg groups showed a statistically significantly greater msDBP reduction than the aliskiren 300 mg group for the ITT population ($p < 0.001$), with further reductions (in LS means) of 3.58 mmHg and 3.12 mmHg, respectively, over the aliskiren 300 mg group. A tabular summary of results is shown in Table 16.

Table 16: Study CSPP100A2332 - Statistical analysis of change from baseline in msDBP at endpoint, (ITT population)

Treatment group	N	LSM change from baseline (SE)	
Aliskiren 300 mg/HCTZ 25 mg	284	- 11.00 (0.551)	
Aliskiren 300 mg/HCTZ 12.5 mg	292	- 10.54 (0.539)	
Aliskiren 300 mg	296	- 7.42 (0.539)	
Pairwise comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-value**
Ali 300 mg/HCTZ 25mg vs. Ali 300 mg	- 3.58 (0.730)	(- 5.01, - 2.15)	< 0.001*
Ali 300 mg/HCTZ 12.5 mg vs. Ali 300 mg	- 3.12 (0.724)	(- 4.54, - 1.70)	< 0.001*

Source: [Study SPP100A2332 PT-Table 14.2-1.1b (M.5, v.107, 5.3.5.1, p.27635)]
SE = standard error, LSM = least squares mean, CI = confidence interval
Least squares means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region and baseline.
P-values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Both aliskiren/HCTZ 300/25 mg and aliskiren/HCTZ 300/12.5 mg groups showed a statistically significantly greater msSBP reduction than the aliskiren 300 mg group for the ITT population ($p < 0.001$), with further reductions (in LS means) of 7.90 mmHg and 5.53 mmHg, respectively, over the aliskiren 300 mg group (see Table 17).

Table 17: Study CSPP100A2332 - Statistical analysis of change from baseline in msSBP at endpoint (ITT population)

Treatment group	N	LSM change from baseline (SE)	
Aliskiren 300 mg/HCTZ 25 mg	284	- 15.85 (0.886)	
Aliskiren 300 mg/HCTZ 12.5 mg	292	- 13.49 (0.867)	
Aliskiren 300 mg	296	- 7.96 (0.866)	
Pairwise comparison	**LSM difference in change from baseline**	**95% CI for LSM difference**	**P-value**
Ali 300 mg/HCTZ 25mg vs. Ali 300 mg	- 7.90	(- 10.20, - 5.59)	< 0.001*
Ali 300 mg/HCTZ 12.5 mg vs. Ali 300 mg	- 5.53	(- 7.82, - 3.25)	< 0.001*

Source: [Study SPP100A2332 PT-Table 14.2-2.1b (M.5, v.107, 5.3.5.1, p.27647)]
SE = standard error, LSM = least squares mean, CI = confidence interval
Least squares means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region and baseline.
P-values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Response rates and control rates

Table 18 shows the between-treatment comparison of blood pressure response at endpoint. Larger proportions of patients in the aliskiren/HCTZ 300/25 mg group (77.11%) and aliskiren/HCTZ 300/12.5 mg group (73.29%) showed blood pressure response compared to the aliskiren 300 mg group (62.16%). Both differences were statistically significant. Results of the between-treatment analysis results of blood pressure control at endpoint data are shown in Table 19. The BP control rates for the three groups were: 40.88% for aliskiren 300 mg, 57.88% for aliskiren/HCTZ 300/12.5 mg, and 60.21% for aliskiren/HCTZ 300/25 mg. The two aliskiren/HCTZ groups had statistically significant higher BP control rates than the aliskiren 300 mg group ($p < 0.001$).

The evaluator noted that the results from Study CSPP100A2332 support the use of aliskiren/HCTZ combination therapy for treatment of hypertension in patients who have not responded to aliskiren monotherapy. The data support a second line indication only, limited to patients pre-treated with aliskiren

Table 18: Study SPP100A2332 - Between treatment comparison for BP response at endpoint (ITT population)

	Treatment A		Treatment B		p-value
Treatment comparison A vs. B	**n / N**	**(%)**	**n / N**	**(%)**	
Ali 300 mg/HCTZ 25 mg vs. Ali 300 mg	219/284	77.11	184/296	62.16	< 0.001*
Ali 300 mg/HCTZ 12.5 mg vs. Ali 300 mg	214/292	73.29	184/296	62.16	0.002*

Source: [Study SPP100A2332 PT-Table 14.2-2.7 (M.5, v.107, 5.3.5.1, p.27658)]
Blood pressure response is defined as a patient with msDBP < 90 mmHg or ≥ 10 mmHg reduction from baseline.
P-values were from a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.
Baseline is the Week 0 value.
N = Number of patients with baseline and Week 8 endpoint msDBP values.
* indicates statistical significance at 0.05 level.

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Table 19: Study SPP100A2332 - Between treatment comparison for BP control at endpoint by treatment group, (ITT population)

	Treatment A		Treatment B		p-value
Treatment comparison A vs. B	**n / N**	**(%)**	**n / N**	**(%)**	
Ali 300 mg/HCTZ 25 mg vs. Ali 300 mg	171/284	60.21	121/296	40.88	< 0.001*
Ali 300 mg/HCTZ 12.5 mg vs. Ali 300 mg	169/292	57.88	121/296	40.88	< 0.001*

Source: [Study SPP100A2332 PT-Table 14.2-2.11 (M.5, v.107, 5.3.5.1, p.27662)]
A patient with control in BP is defined as having a msDBP < 90 mmHg and a msSBP < 140 mmHg.
The control rate was analyzed by using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.
Baseline is the Week 0 value.
* indicates statistical significance at 0.05 level.

Study CSPP100A 2333

Study CSPP100A 2333 provided efficacy data to evaluate the use of aliskiren/HCTZ combination in patients with blood pressure not adequately responding to HCTZ monotherapy. This was an eight-week, randomised, double-blind, parallel group, multicentre study comparing the efficacy and safety of the combination of aliskiren/HCTZ 300/25 mg and 150/25 mg to HCTZ 25 mg alone, in patients with essential hypertension who do not adequately respond to HCTZ monotherapy (msDBP ≥ 90 mmHg and < 110 mmHg after a 4-week treatment with HCTZ 25 mg). The study was comprised of 3 periods: a 4-day washout period, a 4-week single-blind run-in period, and an 8-week randomised double-blind treatment period.

The treatment groups were generally comparable with respect to demographics and baseline characteristics. For the 722 patients randomised to the trial the mean age was 53.5 years, and 14.5% of patients were 65 years or older, while 1.8% were 75 years or older. The HCTZ 25 mg group had a slightly increased number of patients who were 75 years or older (3.7%) compared to 0 .9% for aliskiren/HCTZ 300/25 mg and 0.8% for aliskiren/HCTZ 150/25 mg. Mean exposure was similar in all groups, as were the rates of safety-related discontinuations.

Efficacy Results

msDBP and msSBP

In this study with patients not adequately responsive to HCTZ monotherapy, both aliskiren/HCTZ 300/25 mg and aliskiren/HCTZ 150/25 mg combination groups showed a statistically significantly greater msDBP reduction than the HCTZ 25 treatment group for the ITT population ($p < 0.001$), with further reductions in least squares means (LSMs) of 5.94 mmHg and 3.73 mmHg, respectively, over the HCTZ 25 group. A tabular summary of results is provided in Table 20.

Table 20: Study CSPP100A2333 - Change from baseline in msDBP at endpoint (ITT population)

Treatment group	N	LSM change from baseline (SE)	
Aliskiren 300 mg/HCTZ 25 mg	232	- 10.73 (0.481)	
Aliskiren 150 mg/HCTZ 25 mg	242	- 8.52 (0.471)	
HCTZ 25 mg	244	- 4.80 (0.469)	
Pairwise comparison	**LSM difference in change from baseline**	**95% CI for LSM difference**	**P-value**
Ali 300 mg/HCTZ 25mg vs. HCTZ 25 mg	- 5.94	(- 7.24, - 4.63)	< 0.001*
Ali 150 mg/HCTZ 25 mg vs. HCTZ 25 mg	- 3.73	(- 5.02, - 2.43)	< 0.001*

SE = standard error, LSM = least squares mean, CI = confidence interval
Ali = aliskiren; HCTZ = hydrochlorothiazide
Least squares means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region and baseline.
P-values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Both aliskiren/HCTZ 300/25 mg and aliskiren/HCTZ 150/25 mg combination groups showed a statistically significantly greater msSBP reduction than the HCTZ 25 treatment group for the ITT population ($p < 0.001$), with further reductions in LSMs of 9.63 mmHg and 5.87 mmHg, respectively, over the HCTZ 25 group (see Table 21).

Table 21: Study CSPP100A2333 - Change from baseline in msSBP at endpoint, (ITT population)

Treatment group	N	LSM change from baseline (SE)	
Aliskiren 300 mg/HCTZ 25 mg	232	- 16.69 (0.835)	
Aliskiren 150 mg/HCTZ 25 mg	242	- 12.93 (0.817)	
HCTZ 25 mg	244	- 7.06 (0.814)	
Pairwise comparison	**LSM difference in change from baseline**	**95% CI for LSM difference**	**P-value**
Ali 300 mg/HCTZ 25mg vs. HCTZ 25 mg	- 9.63	(- 11.90, -7.36)	< 0.001*
Ali 150 mg/HCTZ 25 mg vs. HCTZ 25 mg	- 5.87	(- 8.11, - 3.63)	< 0.001*

SE = standard error, LSM = least squares mean, CI = confidence interval;
Ali = aliskiren; HCTZ = hydrochlorothiazide
Least squares means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region and baseline.
P-values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Response rates and control rates

Table 22 shows the between-treatment comparison of blood pressure response at endpoint. More patients in the aliskiren/HCTZ 300/25 mg group (78.45%) and aliskiren/HCTZ 150/25 mg group (67.36%) showed statistically significant ($p < 0.001$) blood pressure response compared to the HCTZ 25 mg group (47.13%).

Blood pressure control was defined as msDBP < 90 mmHg ad msSBP < 140 mmHg. The BP control rates for the 3 groups were: 58.19% for aliskiren/HCTZ 300/25 mg, 48.76% for aliskiren/HCTZ 150/25mg, and 25.82% for HCTZ 25 (see Table 23). Both aliskiren/HCTZ combination groups had statistically significant higher BP control rates than the HCTZ 25 group at endpoint ($p < 0.001$).

The evaluator noted that the results from Study CSPP100A2333 support the use of aliskiren/HCTZ combination therapy for treatment of hypertension in patients who have not responded to HCTZ monotherapy, that is, as a second line therapy, limited to patients pre-treated with HCTZ.

Table 22: Study CSPP100A2333 - Between-treatment comparison for BP response at endpoint (ITT population)

	Treatment A		Treatment B		p-value
Treatment comparison A vs. B	**n / N**	**(%)**	**n / N**	**(%)**	
Ali 300 mg/HCTZ 25 mg vs. HCTZ 25 mg	182/232	78.45	115/244	47.13	< 0.001*
Ali 150 mg/HCTZ 25 mg vs. HCTZ 25 mg	163/242	67.36	115/244	47.13	< 0.001*

Blood pressure response is defined as a patient with msDBP < 90 mmHg or ≥ 10 mmHg reduction from baseline.
p-values were from a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.
Baseline is the Week 0 value.
n = number of patients with response
N = Number of patients with baseline and endpoint msDBP values.
* indicates statistical significance at 0.05 level.
Ali = aliskiren; HCTZ = hydrochlorothiazide

Table 23: Study CSPP100A2333 – Between-treatment comparison for BP control at endpoint (ITT population)

	Treatment A		Treatment B		p-value
Treatment comparison A vs. B	**n / N**	**(%)**	**n / N**	**(%)**	
Ali 300 mg/HCTZ 25 mg vs. HCTZ 25 mg	135/232	58.19	63/244	25.82	< 0.001*
Ali 150 mg/HCTZ 25 mg vs. HCTZ 25 mg	118/242	48.76	63/244	25.82	< 0.001*

A patient with control in BP is defined as having a msDBP < 90 mmHg and a msSBP < 140 mmHg.
The control rate was analyzed by using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.
Baseline is the Week 0 value.
n = number of patients with control
N = Number of patients with baseline and endpoint msDBP values.
* indicates statistical significance at 0.05 level.
Ali = aliskiren; HCTZ = hydrochlorothiazide

Study CSPP100A 2331- Study in patients not adequately responding to HCTZ monotherapy

Study CSPP100A 2331 provided supportive efficacy data for the use of aliskiren/HCTZ combination in patients with blood pressure not adequately responding to HCTZ monotherapy. This was an eight week, randomised, double-blind, parallel-group, multicentre, active control, dose-escalation study in hypertensive patients who were not adequately responsive to HCTZ monotherapy. The study had two periods: a 4 week single-blind run-in with HCTZ (12.5 mg for one week and 25 mg for three weeks) and an 8 week double-blind treatment with either HCTZ 25 mg, aliskiren/HCTZ (150/25 mg for four weeks and 300/25 mg for another four weeks), valsartan/HCTZ (160/25 mg for four weeks and 320/25 mg for another four weeks), or aliskiren/valsartan/HCTZ (150/160/25 mg for four weeks and 300/320/25 mg for another four weeks).

The treatment groups were generally comparable with respect to demographics and baseline characteristics in Study CSPP100A2331. The mean age of patients was 53.2 years with a mean duration of hypertension of 8.4 years. Approximately 15% of patients were 65 years of age or older, and 3% were 75 years of age or older. The valsartan/HCTZ group had a slightly greater mean age (55 years) and a greater proportion of patients ≥ 65 years old (21%) compared to the other three treatment groups. Mean exposure was similar in all groups. The overall discontinuation rate was lowest in the aliskiren/valsartan/HCTZ group (4.2%) and highest in the HCTZ monotherapy group (12.5%). The higher discontinuation rate in the HCTZ group was accounted for by the number of patients who discontinued due to unsatisfactory therapeutic response (4.6%) and loss to follow-up (3.9%) compared to <2% in each of the remaining treatment groups for each reason.

Efficacy Results

msDBP and msSBP

In Study CSPP100A 2331 in patients not adequately responsive to HCTZ monotherapy, aliskiren/HCTZ 300/25 mg produced a statistically significant superior reduction in msDBP and msSBP compared to HCTZ 25 mg alone at Week 8 endpoint (p<0.0001), as shown in Tables 24 and 25.

Table 24: Study CSPP100A2331 - Change from baseline in msDBP at endpoint (ITT population)

Treatment group		N	LSM change from baseline (SE)	
HCTZ		151	-6.4 (0.70)	
Aliskiren/HCTZ		164	-10.5 (0.67)	
Valsartan/HCTZ		154	-13.5 (0.70)	
Aliskiren/valsartan/HCTZ		168	-15.9 (0.67)	
Pairwise comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value[1]**
Aliskiren/valsartan/HCTZ	vs. Aliskiren/HCTZ	-5.4 (0.95)	(-7.27, -3.56)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. Valsartan/HCTZ	-2.4 (0.96)	(-4.31, -0.52)	0.0124*
Aliskiren/HCTZ	vs. HCTZ	-4.1 (0.97)	(-6.05, -2.23)	<0.0001*
Valsartan/HCTZ	vs. HCTZ	-7.1 (0.99)	(-9.08, -5.20)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. HCTZ	-9.6 (0.97)	(-11.46, -7.65)	<0.0001*

SE = Standard Error; LSM = Least Square Mean; CI = Confidence Interval
Least square mean, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
[1] p-values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.
Note: Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).

Table 25: Study CSPP100A2331 - Change from baseline in msSBP at endpoint (ITT population)

Treatment group		N	LSM change from baseline (SE)	
HCTZ		151	-6.3 (1.12)	
Aliskiren/HCTZ		164	-15.0 (1.08)	
Valsartan/HCTZ		154	-18.3 (1.12)	
Aliskiren/valsartan/HCTZ		168	-21.6 (1.07)	
Pairwise comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value[1]**
Aliskiren/valsartan/HCTZ	vs. Aliskiren/HCTZ	-6.5 (1.51)	(-9.51, -3.57)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. Valsartan/HCTZ	-3.3 (1.55)	(-6.31, -0.23)	0.0350*
Aliskiren/HCTZ	vs. HCTZ	-8.7 (1.55)	(-11.79, -5.68)	<0.0001*
Valsartan/HCTZ	vs. HCTZ	-12.0 (1.58)	(-15.11, -8.90)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. HCTZ	-15.3 (1.55)	(-18.31, -12.2)	<0.0001*

SE = Standard Error; LSM = Least Square Mean; CI = Confidence Interval.
Least square mean, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
[1] p-values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.
Note: Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).

Response rates and control rates

The aliskiren/HCTZ (300/25 mg) group had a control rate of 40.9% (target of < 140/90 mmHg), which was significantly higher than that found in the HCTZ monotherapy (20.5%). A tabular summary of results is provided in Table 26. At Week 8 endpoint, the proportion of patients that met the responder criteria (msDBP < 90 mmHg, and/or a ≥ 10 mmHg reduction from baseline) for the aliskiren/HCTZ (300/25 mg) group was 64.0% (p=0.0004), compared to the HCTZ monotherapy group (39.1%) .

Exploratory Analyses - Biomarkers

In Study SPP100A2331 biomarkers were analysed. Using the geometric mean of the post-baseline over baseline ratio, renin was decreased 4.2% by HCTZ, and increased 389.1%, 348.5% and 1464.3% by aliskiren/HCTZ, valsartan/HCTZ and aliskiren/valsartan/HCTZ, respectively. Plasma renin activity was reduced by aliskiren/HCTZ (-78.2%) and increased by valsartan/HCTZ (380%) Neither HCTZ monotherapy nor triple combination therapy effected PRA.

Table 26: Study CSPP100A2331 – Between-treatment comparison for BP control rate at endpoint (ITT population)

Pairwise comparison		Treatment A	Treatment B	
A	vs. B	n/N (%)	n/N (%)	p-value
Aliskiren/valsartan/HCTZ	vs. Aliskiren/HCTZ	112/168 (66.7)	67/164 (40.9)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. Valsartan/HCTZ	112/168 (66.7)	75/154 (48.7)	0.0026*
Aliskiren/HCTZ	vs. HCTZ	67/164 (40.9)	31/151 (20.5)	0.0002*
Valsartan/HCTZ	vs. HCTZ	75/154 (48.7)	31/151 (20.5)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. HCTZ	112/168 (66.7)	31/151 (20.5)	<0.0001*

A patient with control in BP is defined as having a msDBP <90 mmHg and a msSBP <140 mmHg.
The control rate was analyzed by using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.
n = number of patients with control
N = Number of patients with baseline and endpoint msDBP values.
Note: Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).
* Indicates statistical significance at 0.05 level.

The evaluator noted that the results from Study CSPP100A2331 support the use of aliskiren/HCTZ combination therapy as second line treatment of hypertension in patients who have not responded to HCTZ monotherapy.

Study CSPP100A 2309

Study CSPP100A2309 provided efficacy data to evaluate the use of aliskiren/HCTZ combination in obese hypertensive patients with blood pressure not adequately responding to HCTZ monotherapy. This was a 12-week, randomised, double-blind, parallel group study to evaluate the efficacy and safety of the combination of aliskiren with HCTZ 25 mg compared to irbesartan or amlodipine with HCTZ 25 mg or HCTZ 25 mg alone in hypertensive patients with BMI $\geq$ 30 kg/m^2 who were not adequately responsive to HCTZ 25 mg monotherapy. After 4-weeks treatment with HCTZ 25 mg, patients who were not adequately responsive (msDBP $\geq$ 90 and < 110 mmHg) were randomised to one of the 4 treatment groups: HCTZ 25 mg monotherapy, combination therapies of aliskiren/HCTZ (150/25 mg), irbesartan/HCTZ (150/25 mg) or amlodipine/HCTZ (5/25 mg) for the initial 4 weeks. The doses in the combination groups were force-titrated to aliskiren/HCTZ 300/25 mg, irbesartan/HCTZ 300/25 mg, or amlodipine/HCTZ 10/25 mg) for another 8 weeks. The total duration of the double-blind treatment was 12 weeks and the primary efficacy endpoint was assessed at 8 weeks post treatment.

Baseline characteristics in Study CSPP100A2309 were comparable across treatment groups in which included obese patients only. The average age ranged from 53.0 years in the irbesartan/HCTZ group to 55.2 years in the amlodipine/HCTZ and the HCTZ groups. There were more patients $\geq$ 65 years of age in the amlodipine/HCTZ and the HCTZ groups. Mean exposure was similar in all the treatment groups.

Efficacy results

msDBP and msSBP

Tabular summaries of results are provided in Tables 27 and 28. In this study with obese hypertensive patients not adequately responsive to HCTZ monotherapy, aliskiren/HCTZ 300/25 mg produced a statistically significant superior reduction in msDBP and msSBP compared to HCTZ 25 mg alone at Week 8 endpoint ($p<0.0001$). Comparisons with irbesartan/HCTZ and amlodipine/HCTZ combinations were numerically greater; however the differences were not statistically significant.

Table 27: Study CSPP100A2309 - Between-treatment analysis for change from baseline in msDBP at Week 8 endpoint in (ITT population)

Treatment group	N	LSM change from baseline (SE)	
Aliskiren 300 mg / HCTZ 25 mg	113	-11.91 (0.74)	
Irbesartan 300 mg / HCTZ 25 mg	117	-11.33 (0.72)	
Amlodipine 10 mg / HCTZ 25 mg	122	-10.30 (0.71)	
HCTZ 25 mg	117	-7.89 (0.73)	
Pairwise comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
Aliskiren 300 mg / HCTZ 25 mg vs. HCTZ 25 mg	-4.02 (1.02)	(-6.02, -2.01)	<.0001*
Aliskiren 300 mg / HCTZ 25 mg vs. Irbesartan 300 mg / HCTZ 25 mg	-0.57 (1.02)	(-2.58, 1.43)	0.5757
Aliskiren 300 mg / HCTZ 25 mg vs. Amlodipine 10 mg / HCTZ 25 mg	-1.60 (1.01)	(-3.59, 0.38)	0.1135

SE=Standard Error; LSM=Least Square Mean; CI=Confidence Interval.
[1]P-values and treatment comparisons were evaluated using an ANCOVA model containing treatment, region and centered baseline.

* Indicates statistical significance at 0.05 level.

Table 28: Study CSPP100A2309 - Between-treatment analysis for change from baseline in msSBP at Week 8 endpoint (ITT population

Treatment group	N	LSM change from baseline (SE)	
Aliskiren 300mg / HCTZ 25mg	113	-15.79 (1.01)	
Irbesartan 300mg / HCTZ 25mg	117	-15.44 (1.00)	
Amlodipine 10mg / HCTZ 25mg	122	-13.55 (0.98)	
HCTZ 25mg	117	-8.62 (1.00)	
Pairwise comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
Aliskiren 300mg / HCTZ 25mg vs. HCTZ 25mg	-7.17 (1.40)	(-9.93, -4.41)	<.0001*
Aliskiren 300mg / HCTZ 25mg vs. Irbesartan 300mg / HCTZ 25mg	-0.35 (1.40)	(-3.11, 2.40)	0.8006
Aliskiren 300mg / HCTZ 25mg vs. Amlodipine 10mg / HCTZ 25mg	-2.24 (1.39)	(-4.97, 0.49)	0.1071

SE=Standard Error; LSM=Least Square Mean; CI=Confidence Interval.
[1]P-values and treatment comparisons were evaluated using an ANCOVA model containing treatment, region and centered baseline.

* Indicates statistical significance at 0.05 level.

Response rates and control rates

In Study CSPP100A2309, response rates for the combination therapies ranged from 73.5% for aliskiren/HCTZ to 68% for amlodipine/HCTZ, despite the resistant nature of hypertension in the obese. The response rate for the aliskiren/HCTZ combination treatment at Week 8 endpoint (73.5%) was statistically superior compared with HCTZ 25 mg alone (59.0%) ($p=0.0193$). Similar results were achieved at Week 12 endpoint ($p=0.0034$). The response rate in the aliskiren/HCTZ group at Week 8 endpoint was numerically greater, however the differences were not statistically different

from irbesartan/HCTZ (70.9%) or amlodipine/HCTZ (68.0%). Results were similar at Week 12 endpoint.

Plasma renin activity (PRA)

Patients in Study CSPP100A2309 had lower baseline renin values than typical hypertension patients. As expected, PRA was significantly decreased by aliskiren/HCTZ (-62.2%) and significantly increased by irbesartan/HCTZ (238.8%) and amlodipine/HCTZ (76.5%). It showed a non-significant decrease of 11.7% with continued HCTZ treatment.

The evaluator noted that the data support the use of the combination of aliskiren with hydrochlorothiazide as a second line therapy, limited to obese patients pre-treated with hydrochlorothiazide.

Study CSPP100A 2303

Study CSPP100A2303 provided efficacy data in relation to the use of the aliskiren regimen (including the combination with HCTZ) in severe hypertensive patients. This was an 8-week, randomised, double-blind, parallel group, multicentre study to evaluate the safety and efficacy of aliskiren with the optional addition of HCTZ compared to lisinopril with the optional addition of HCTZ in patients with uncomplicated severe hypertension. After washout and placebo run-in, eligible patients with severe hypertension (msDBP ≥ 105 and < 120 mmHg) were randomised in a 2:1 ratio to aliskiren or lisinopril treatment. The starting doses were 150 mg for aliskiren and 20 mg for lisinopril. The doses were increased to aliskiren 300 mg or lisinopril 40 mg after 1 week of double-blind therapy if msDBP was ≥ 110 mmHg or msSBP was ≥ 180 mmHg, and after 2 weeks of treatment if the msSBP was ≥ 160 mmHg or msDBP was ≥ 95 mmHg. Subsequently, HCTZ 25 mg was added to aliskiren 300 mg or lisinopril 40 mg at any visit if msSBP remained ≥ 160 mmHg or msDBP was ≥ 95 mmHg.

Patients in the treatment regimens in Study CSPP100A2303 were generally comparable with respect to demographics and baseline characteristics. The mean age of patients overall was 55 years. The mean duration of hypertension overall was 9 years. Baseline msDBP and msSBP were higher in Study CSPP100A2303 reflecting the inclusion of only patients with severe hypertension. Mean exposure was similar in both groups and safety-related discontinuations occurred at similar low rates for both groups.

Efficacy results

Of the 125 patients in the aliskiren treatment regimen, most titrated from 150 mg to 300 mg (92 patients, or 73.6%), and more than half (67 patients, or 53.6%) added on 25 mg HCTZ. Of the 58 patients in the lisinopril treatment regimen, most titrated from 20 mg to 40 mg (38 patients, or 65.5%), and almost half (26 patients, or 44.8%) added on 25 mg HCTZ.

msDBP and msSBP

Results for mean sitting diastolic BP and mean sitting systolic BP in Study CSPP100A2303 are shown in Tables 29 and 30. Both treatment regimens produced reductions from baseline in msDBP and msSBP at all time points. The reductions were numerically greater in the lisinopril treatment group than the aliskiren group. HCTZ treatment was allowed as add-on therapy at or after Visit 5. Both msDBP and msSBP in the aliskiren regimen showed further reductions observed at the subsequent visits after Visit 5. Once again the changes from baseline in msDBP and msSBP at endpoint were numerically greater for the lisinopril treatment regimen.

Response rates

Blood pressure response in this active-controlled Study CSPP100A2303 was defined in the same way as in the placebo-controlled (Study CSPP100A22040). Blood pressure control was not

measured in Study CSPP100A2303. In patients with severe hypertension, the percentage of responders was 81.5% with the aliskiren regimen and 87.9% with the lisinopril.

Table 29: Study CSPP100A2303 - Changes from baseline in msDBP at double-blind visit by randomised treatment group in Study CSPP100A2303 (ITT population)

		Aliskiren regimen		Lisinopril regimen	
Visit	Day	N*	Mean (SD)	N*	Mean (SD)
3	1	124		58	
4	7	124	-10.1 (8.6)	58	-11.0 (8.6)
5	14	123	-13.3 (8.6)	58	-15.0 (10.2)
6	28	118	-16.1 (9.2)	57	-17.7 (9.8)
7	42	115	-19.4 (8.7)	56	-18.5 (9.2)
8	56	113	-19.1 (8.4)	54	-20.0 (8.0)
Endpoint**		124	-18.5 (8.7)	58	-20.1 (7.9)

(*) N is the number of patients with values at both baseline and post-baseline visit.
(**) Endpoint is Day 56, or last visit carried forward.
Note: A decrease in the mean change indicates improvement

Table 30: Study CSPP100A2303 - Changes from baseline in msSBP at double-blind visit (ITT population)

		Aliskiren regimen		Lisinopril regimen	
Visit	Day	N*	Mean (SD)	N*	Mean (SD)
3	1	124		58	
4	7	124	-8.2 (13.3)	58	-10.9 (13.3)
5	14	123	-12.5 (13.7)	58	-13.4 (15.3)
6	28	118	-15.7 (15.1)	57	-18.7 (15.0)
7	42	115	-20.0 (13.7)	56	-20.2 (14.2)
8	56	113	-21.2 (15.0)	54	-23.0 (14.6)
Endpoint**		124	-20.0 (15.3)	58	-22.3 (14.6)

(*) N is the number of patients with values at both baseline and post-baseline visit.
(**) Endpoint is Day 56, or last visit carried forward.
Note: A decrease in the mean change indicates improvement

Study CSPP100A2302 and Study CSPP100A2302E1

This was an open-label, multicentre, randomised, parallel-group, dose escalation study of aliskiren 150 mg and 300 mg administered as monotherapy, and aliskiren 300 mg administered with HCTZ 12.5 mg or 25 mg as needed for BP control in patients with uncomplicated essential hypertension. The study was comprised of three periods (with an additional Period 4 in a subset of patients at selected centres). Period 1 was a 1 to 2 week period during which patients taking antihypertensives tapered off their medication. Patients who were newly diagnosed with uncomplicated hypertension and who were not taking any antihypertensive medication(s), or those who had not been taking antihypertensive drugs for at least 1 week prior to Visit 1, could combine visits one and two and be enrolled directly into the two to four week screening period.

Period 2 was a 2 to 4 week drug-free screening period used to establish a baseline blood pressure and eligibility for randomisation (based on the inclusion and exclusion criteria). Qualified patients were randomised to either aliskiren 150 mg or 300 mg once daily (3:2 ratio) for 52 weeks of open-label treatment (Period 3). Patients began taking their open-label study medication (aliskiren 150 mg or 300 mg) at Visit 3. At Visits 5 and 6 (end of treatment month 2 and 3), investigators could adjust individual therapy in order to achieve a goal BP of < 140/90 mmHg. At these visits, aliskiren 150 mg could be increased to 300 mg. Patients receiving aliskiren 300 mg could add HCTZ 12.5 mg, and patients receiving aliskiren 300 mg with HCTZ 12.5 mg could increase the dose of HCTZ

to 25 mg in order to reach the target BP of < 140/90 mmHg. At visit 7 (end of treatment month 4) and thereafter, up-titration to the next treatment step could only occur if the patient's BP was persistently (2 consecutive visits) ≥ 140/90 mmHg.

Following 11 months of active, open-label treatment, it was planned that the first 320 patients receiving aliskiren as monotherapy for the treatment of their hypertension who consented to participate, at selected centres, would be randomised to the one month, double-blind, placebo-controlled withdrawal phase (Period 4). Patients were stratified based on dose and randomised in a 1:1 ratio to either continue their current treatment of aliskiren monotherapy or to placebo.

Study CSPP100A2302E1 was a 4 month, open-label extension period for a subset of patients at selected centres who completed at least 8 months of open-label combination therapy with aliskiren 300 mg and HCTZ 25 mg in the CSPP100A2302 core study. At Visit 10, Month 12, all Visit 10 (final visit for the CSPP100A2302 core study) assessments were performed and the study completion page for the core study was completed. After completion of these procedures, approximately 250 patients from selected centres who completed at least 8 months of treatment with aliskiren 300 mg combined with HCTZ 25 mg were offered the opportunity to participate in the 4 month extension of the study. After signing an informed consent, patients were dispensed sufficient medication for 4 months of treatment and were asked to return to the clinic for a final visit (Visit 15) at the end of the 4-month extension (month 16). For efficacy analyses, the endpoint was at 12 months for Study CSPP100A2302 and 16 months for Study CSPP100A2302E1.

There were 1625 patients who completed the open-label period (83.1%), and 330 who discontinued (16.9%). A subset of 261 completed patients participated in the randomised withdrawal period; 250 patients (95.8%) completed the randomised withdrawal period, and 11 (4.2%) discontinued. The treatment groups in the open-label randomised population were generally comparable with respect to the demographics and background characteristics. In both aliskiren treatment groups, the majority of the patients were Caucasian (86.3%), and there was a slight majority of male patients (52.5%). The overall mean age was 55.8 years, with most patients younger than 65 years of age (77.5%). There were few diabetics, and less than half of the patients met the criteria for metabolic syndrome. Approximately one third was obese (BMI ≥ 30 kg/m^2). The mean duration of hypertension was 7.3 years.

Examination of the demographics and background characteristics showed important differences between the patients who remained on monotherapy throughout the study and the patients who were titrated to combination therapy in the open-label period. Combination therapy patients were slightly older than monotherapy patients (mean age of 57.0 vs. 54.8 years), had a longer duration of hypertension (8.2 vs. 6.5 years), and included more males (55.3% vs. 50.3%), obese patients (41.6% vs. 34.3%) and those with metabolic syndrome (47.7% vs. 41.7%). The baseline blood pressures were higher in the combination therapy group than in the monotherapy group (msDBP: 98.4 mmHg vs 96.7 mmHg; msSBP: 156.1 mmHg vs 150.5 mmHg).

Efficacy results

msDBP and msSBP

Mean changes from baseline in msDBP and msSBP for patients receiving combination therapy and monotherapy in Study CSPP100A2302 are summarised in Table 31. Both the combination therapy and monotherapy produced reductions in msDBP and msSBP from baseline and the BP lowering effect was maintained throughout the whole study duration. According to the study design, all patients who received HCTZ as add-on treatment were those whose BP was not adequately controlled by aliskiren monotherapy. In this cohort of patients, the addition of HCTZ did produce further BP reductions.

Table 31: Study CSPP100A2302 - Mean change from baseline in msDBP and msSBP at open-label visit by treatment received in long-term study (ITT population)

Open-label Visit	Month	Monotherapy*** N = 1060			Combo*** N = 868		
			Change (SD)			Change (SD)	
		N*	msDBP	msSBP	N*	msDBP	msSBP
4	1	1059	-10.5 (7.8)	-13.6 (12.4)	868	-6.5 (7.1)	-8.9 (12.6)
5	2	990	-12.3 (7.3)	-16.9 (12.2)	866	-6.0 (7.5)	-9.0 (12.4)
6	3	946	-13.9 (7.1)	-19.5 (12.1)	860	-8.6 (7.7)	-12.8 (14.1)
7	4	912	-14.5 (6.6)	-20.1 (11.7)	849	-10.4 (7.8)	-16.4 (14.3)
8	6	901	-14.3 (6.6)	-19.8 (12.1)	832	-11.4 (7.7)	-18.1 (14.7)
9	9	890	-14.7 (6.9)	-19.9 (12.3)	800	-12.6 (7.7)	-20.3 (14.2)
10	11/12	875	-14.7 (7.2)	-19.5 (12.6)	764	-12.8 (7.8)	-19.8 (13.8)
Endpoint**		1060	-13.3 (8.5)	-17.4 (14.5)	868	-12.1 (8.4)	-18.7 (14.6)

Note: A decrease in the mean change indicates improvement.
*N is the number of patients with values obtained at both baseline and post-baseline visit.
**Endpoint is Month 11/12, or last visit carried forward.
***Monotherapy patients are those who never took HCTZ. Combo = combination therapy (patients who took HCTZ at least once).

Results during the extension, Study CSPP100A2302E1, showed that the BP reductions were generally maintained during the 4 months of the extension after being treated with at least eight months of aliskiren/HCTZ 300/25 mg. Results for the core study and the extension period are shown in Table 32.

Table 32: Study CSPP100A2302 and CSPP100A2302E1- Change from baseline (V3) in mean sitting systolic blood pressure (mmHg) during the entire study (All extension population)

			Aliskiren+HCTZ300/25mg		
Visit	Open label month	N*	Baseline (SD)	Mean (SD)	Change (SD)
7	Month 4	198	158.99 (11.44)	143.7 (13.42)	-15.25 (14.17)
8	Month 6	198	158.99 (11.44)	141.1 (13.59)	-17.89 (15.50)
9	Month 9	198	158.99 (11.44)	139.6 (13.84)	-19.35 (14.16)
10	Month 12	198	158.99 (11.44)	140.6 (13.98)	-18.41 (13.84)
15	Month 16	195	159.32 (11.17)	142.1 (14.70)	-17.22 (15.37)
Endpoint**	Month 16	198	158.99 (11.44)	141.7 (15.02)	-17.30 (15.27)

Source: PTT 14.2-1.2
(*) N is the number of patients with values obtained at both baseline and post-baseline visit.
For patients rolled over from study 2203, baseline in 2203 is used.
(**) Endpoint is Month 16, or last visit carried forward.
Note: A decrease in the mean change indicates improvement.

Response rates and control rates

At the endpoint of the open-label treatment in Study CSPP100A2302 the response rate was 80.5% and the control rate was 61.2% for patients in the intent-to-treat population. At the endpoint of the extension, Study CSPP100A2302E1, the response rate was 65.2% and the control rate was 33.3% (see Table 33). Study CSPP100A2302E1 was designed to obtain 12-month safety data in patients receiving the combination of aliskiren/HCTZ 300/25 mg. Patients who were enrolled in the extension study were those whose BP was not adequately controlled by the combination of aliskiren/HCTZ 300/12.5 mg, and therefore patients in this study had hypertension that was more difficult to control. This may explain the lower response rate in the study. Patient numbers were also lower in the extension study.

The evaluator noted that in this study no comparisons were made between the aliskiren monotherapy group and the aliskiren/HCTZ combination group because the two subpopulations were different. It is therefore difficult to draw firm conclusions in relation to whether combination therapy is in fact superior to monotherapy in reducing blood pressure in the longer term.

Table 33: Study CSPP100A2302E1 -Number (%) of responders and controlled patients at endpoint during the entire study (All extension population)

	Aliskiren + HCTZ 300/25 mg n/N (%)
Responders	129/198 (65.2)
Controlled patients	66/198 (33.3)

A Responder was defined as a patient with trough MSDBP < 90 mmHg and/or at least 10 mmHg reduction from baseline.
Control is defined as a mean sitting diastolic blood pressure < 90 mmHg and the mean sitting systolic blood pressure < 140 mmHg.
N = Number of patients with baseline (V3) and endpoint MSDBP values
For patients rolled over from study 2203, baseline in 2203 was used

Plasma renin activity (PRA) and renin concentration (RC)

In Study CSPP100A2302 similar geometric mean decreases from baseline in PRA were observed during the open-label period in patients on monotherapy and combination therapy. At endpoint, the reductions from baseline were 68% and 65.4%, respectively. During the open-label period, patients on monotherapy and combination therapy exhibited increases from baseline in RC. At endpoint, the increase was 176% for monotherapy and 411% for combination therapy, suggesting an additive effect of aliskiren and HCTZ on blockade of the renin angiotensin system. PRA and RC were not measured during the extension Study CSPP100A2302E1.

Study CSPP100A2306

Study CSPP100A2306 was a 26-week, randomised, double-blind, multicentre, parallel group study comparing aliskiren to ramipril in patients with mild to moderate hypertension. Since a substantial number of patients in this study received the HCTZ add-on to aliskiren, the data from the study provide information on efficacy and safety of the aliskiren/HCTZ combination. The addition of HCTZ was permitted in patients whose blood pressure was not adequately controlled (BP $\geq$ 140/90 mmHg) after at least 12 weeks of monotherapy treatment if they were receiving aliskiren 300 mg or ramipril 10 mg. HCTZ was added in a total of 193 patients (45.8%) in the aliskiren group and 209 patients (49.5%) in the ramipril group. The 26-week active treatment was followed by a 4-week double-blind, randomised, placebo-controlled withdrawal period, during which patients were equally randomised to continue on the active treatment or to receive placebo.

A total of 193 (45.8%) patients in the aliskiren group received combination treatment with aliskiren/HCTZ and 209 (49.5%) patients in the ramipril group received ramipril/HCTZ. A total of 92 (21.9%) patients in the aliskiren regimen were titrated from 12.5 to 25 mg HCTZ and 132 (31.3%) patients in the ramipril regimen were titrated from 12.5 to 25 mg HCTZ

Efficacy results

The comparison between aliskiren and ramipril regimens was performed at Week 26 endpoint (aliskiren 150 - 300 mg with optional addition of HCTZ 12.5/25 mg vs ramipril 5 - 10 mg with optional addition of HCTZ 12.5/25 mg) to assess the efficacy of 6 months of treatment between these two regimens.

msDBP and msSBP

In Study CSPP100A2306 both aliskiren and ramipril treatment regimens produced clinically meaningful reductions from baseline in msDBP and msSBP at all time, as shown in Tables 34 and 35. HCTZ treatment was allowed as add-on at or after Week 12. Both msDBP and msSBP in aliskiren regimen showed further reductions observed at the subsequent visits after Week 12. The aliskiren-based treatment regimen produced statistically significant superior reductions in both msDBP and msSBP compared to the ramipril-based treatment regimen at the Week 26 Endpoint.

Table 34: Study CSPP100A2306 - Change from baseline in msDBP at Week 26 endpoint in active-controlled treatment period (ITT population)

Treatment regimen	N	LSM change from baseline(SE)		
Aliskiren	414	-13.17 (0.39)		
Ramipril	418	-11.96 (0.38)		
			P-value[1]	
Pairwise comparison	LSM difference in Change from baseline (SE)	95% CI for LSM difference	Non-inferiority+	Superiority
Aliskiren vs. Ramipril	-1.21 (0.54)	(-2.27,-0.15)	<.0001*	0.0250*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval.
+Non-inferiority margin used in the non-inferiority test is 2 mmHg. One-sided significance level of 0.025 was only used for the non-inferiority test.
[1]P-Values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Table 35: Study CSPP100A2306 - Change from baseline in msSBP at Week 26 endpoint in active-controlled treatment period (ITT population)

Treatment regimen	N	LSM change from baseline(SE)		
Aliskiren	414	-17.88 (0.65)		
Ramipril	418	-15.24 (0.64)		
			P-value[1]	
Pairwise comparison	LSM difference in Change from baseline (SE)	95% CI for LSM difference	Non-inferiority+	Superiority
Aliskiren vs. Ramipril	-2.64 (0.90)	(-4.41,-0.86)	<.0001*	0.0036*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval.
+Non-inferiority margin used in the non-inferiority test is 4 mmHg. One-sided significance level of 0.025 was only used for the non-inferiority test.
[1]P-Values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Response rates and control rates

Higher response rates were observed in the aliskiren regimen compared with the ramipril regimen at Week 26 endpoint in Study CSPP100A2306. The proportion of patients controlled to a target blood pressure of < 140/90 mmHg on the aliskiren-based antihypertensive regimen was statistically greater than that on the ramipril-based regimen at Week 26 endpoint (p=0.0205).

Summary of efficacy

The efficacy data submitted for evaluation have demonstrated the efficacy of the combination of aliskiren/HCTZ in the treatment of hypertension, with superiority of the claimed doses compared to placebo or the respective monotherapy. The majority of the studies assessed efficacy when used in patients who had failed to respond to monotherapy with aliskiren or HCTZ alone.

Importantly, patients with severe or secondary hypertension were excluded in all studies except for study CSPP100A2303, in which the patient population had severe hypertension. Patients were also generally excluded from studies if they had recent or ongoing cardiovascular or cerebrovascular disorders that would preclude even brief periods off antihypertensive treatment used for either BP control or protection against morbidity and mortality. The clinical studies also excluded most patients with severe renal or hepatic impairment or poorly controlled diabetes.

In the general hypertensive population the combination of aliskiren/HCTZ provided superior diastolic and systolic blood pressure lowering effects compared to aliskiren and HCTZ administered as monotherapy in patients with essential hypertension (Study CSPP100A2204). Efficacy of all of the combination doses proposed for registration (150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg) was demonstrated. A positive dose response relationship was demonstrated within the studied dose range of the combination of aliskiren/HCTZ (Study CSPP100A2204).

In the subgroup of patients with severe hypertension:

- Study CSPP100A2303 was the only study conducted specifically in patients with severe hypertension
- The aliskiren-based regimen (with optional addition of HCTZ) produced clinically significant reductions in both diastolic and systolic blood pressure in patients with severe hypertension in Study CSPP100A2303; however results indicated that lisinopril may be more effective than aliskiren in this population.

In relation to long- term efficacy:

- The combination of aliskiren/HCTZ provided long-term efficacy with persistent blood pressure reduction over 12 months of treatment of hypertension (Study CSPP100A2302 and Study CSPP100A2302E1)
- The persistence of effect of aliskiren/HCTZ was demonstrated in patients who remained on the aliskiren/HCTZ combination compared with those who discontinued the treatment (switched to placebo) (Study CSPP100A2306).

Hypertensive patients not adequately responding to either aliskiren or HCTZ monotherapy:

- The combination of aliskiren/HCTZ produced clinically and statistically significant additional reductions in both diastolic and systolic blood pressure and additional blood pressure control and responder rates in patients with essential hypertension not adequately responsive to aliskiren 300 mg monotherapy (Study CSPP100A2332)
- The combination of aliskiren/HCTZ produced clinically and statistically significant additional reductions in both diastolic and systolic blood pressure and additional blood pressure control and responder rates in patients with essential hypertension not adequately responsive to HCTZ 25 mg monotherapy (Study CSPP100A2333 and Study CSP100A2331).

These data support a second line indication for aliskiren/HCTZ, not a first line indication.

Only one study enrolled patients who were treated with antihypertensives as combination therapy and as initial therapy. In initial therapy:

- When used as initial therapy in patients with Stage 2 hypertension, the combination of aliskiren/HCTZ, at most doses proposed for registration as initial therapy, produced significantly greater diastolic and systolic blood pressure reductions and response rates than each of the respective monotherapies (Study CSPP100A2204)
- Notably however, the aliskiren/HCTZ 150/25 mg dose was not shown to be superior to HCTZ 25 mg alone (p =0.0956; M5, v175, p621)
- In Stage 2 patients with additional CV risk, several of the results did not establish that combination therapy with aliskiren/HCTZ was statistically significantly superior to monotherapy. In particular:

- aliskiren/HCTZ 150/12.5 mg was not superior to aliskiren 150 mg alone
- aliskiren/HCTZ 150/25 mg was not superior to aliskiren 150 mg alone
- aliskiren/HCTZ 300/12.5 mg was not superior to aliskiren 300 mg alone
- aliskiren/HCTZ 300/12.5 mg was not superior to HCTZ 12.5 mg alone
- aliskiren/HCTZ 300/12.5 mg was not superior to placebo
- aliskiren/HCTZ 300/25 mg was not superior to aliskiren 300 mg alone

- In relation to blood pressure control in patients who had additional CV risks, the blood pressure control measure of msSBP <130 mmHg and msDBP <80 mmHg was assessed. Results for the percentage of patients achieving control of blood pressure measured by msDBP showed that the combinations of aliskiren/HCTZ 150/12.5mg and 300/12.5mg were significantly superior to aliskiren monotherapy, but not HCTZ monotherapy. When the

msSBP control <130 mmHg rate was assessed in patients with additional CV risk, the aliskiren/HCTZ combination doses proposed for registration demonstrated statistically significantly greater control rates than each of the respective monotherapies with the exception of the 150/25mg dose in which the comparison to HCTZ 25mg was not statistically significant (P=0.081).

The evaluator was of the opinion that the data submitted for evaluation are sufficient to support use of aliskiren/HCTZ for treatment of hypertension in patients whose blood pressure is not adequately controlled on monotherapy, and as replacement therapy in patients already receiving aliskiren and hydrochlorothiazide from separate tablets at the same dose levels. The results from the studies do not adequately support use of aliskiren/HCTZ as initial therapy as proposed by the sponsor. Efficacy results when the combination was administered as initial therapy in patients with markedly elevated blood pressure and additional CV risk do not support first line use of the combination. Insufficient data have been provided that demonstrate superior clinical efficacy of the product given as a first line treatment. In the clinical programme there were not substantial numbers of patients enrolled in studies to support the proposed first line indication. Most clinical studies excluded patients with severe hypertension, poorly controlled diabetes, or significant cardiovascular disease, or cerebrovascular diseases, or renal impairment. Results in the small subgroup of hypertensive patients with additional cardiovascular risk indicated that the percentage of patients controlled by the combination aliskiren/HCTZ was not significantly higher than that obtained by monotherapy treatments. Only limited data were submitted for the first line indication of aliskiren/HCTZ, therefore, the use of the aliskiren/HCTZ combination should be approved only for the second line indications.

Safety

Extent of exposure

The sponsor presented safety data from all studies. Overall, 8472 patients were included in the aliskiren/HCTZ clinical development program, with 3939 being exposed to aliskiren in combination with HCTZ. For the 3939 patients that received aliskiren in combination with HCTZ in the nine completed short-term and long-term studies, the duration of exposure is summarised for each treatment group in Table 36.

For analyses, the sponsor grouped data into four groups as follows:

- Group A which included one double-blind placebo-controlled short-term study Study CSPP100A2204
- Group B which includes StudyCSPP100A2204 plus five double-blind active-controlled short-term studies; Studies CSPP100A2332, CSPP100A2333 CSPP100A2309, CSPP100A2331, and CSPP100A2303
- Group C which includes one open-label long-term study StudyCSPP100A 2302 and its extension Study CSPP100A 2302E1, and
- Group D which includes one double-blind active-controlled long-term study Study CSPP100A 2306

Study SPP100A2302 and its extension SPP100A2302E1 are relevant for the combination aliskiren/HCTZ and report safety data as requested by applicable guidelines (the EU guideline *33CC6a Clinical Investigation of Medicinal Products for Long-Term Use*). In the studies there were 190 patients with aliskiren/HCTZ exposure for more than 360 days (1 year), and 734 patients with aliskiren/HCTZ exposure for more than 180 days (6 months).

Withdrawals

Participation and withdrawals were summarised for the placebo-controlled studies and for the short-term controlled studies. Results in both datasets were comparable. More patients in the placebo

group discontinued treatment early compared with the other groups, mostly due to a higher rate of withdrawal for unsatisfactory therapeutic effect. Discontinuation rates were generally comparable for patients on aliskiren/HCTZ combination therapy compared to those that received the monotherapy components. Participation and withdrawals for the long-term open-label studies and for the long-term double-blind studies were also comparable.

Table 36: Summary statistics for duration of exposure to study drug after randomisation - all studies*

	Number of	Duration of exposure (days)		
Treatment Group	Patients	Mean (SD)	Median	Range
Placebo	193	52.5 (13.2)	56	2 - 83
Mono Ali	3349	153.6 (130.2)	85	1 - 426
Mono HCTZ	1083	56.7 (14.0)	56	1 - 93
Ali/HCTZ 75/6.25 mg	188	54.7 (10.3)	56	1 - 94
Ali/HCTZ 75/12.5 mg	190	53.5 (11.5)	56	4 - 70
Ali/HCTZ 75/25 mg	186	53.9 (10.3)	56	2 - 70
Ali/HCTZ 150/6.25 mg	174	53.7 (12.5)	56	2 - 105
Ali/HCTZ 150/12.5 mg	206	66.2 (50.8)	56	7 - 335
Ali/HCTZ 150/25 mg	722	43.9 (18.5)	54	1 - 302
Ali/HCTZ 300/12.5 mg	1510	101.7 (94.4)	56	1 - 343
Ali/HCTZ 300/25 mg	1576	111.6 (116.8)	56	1 - 448
Ali/HCTZ	3939	105.3 (103.9)	56	1 - 471
Amlodipine/HCTZ	127	80.3 (14.8)	84	3 - 92
ACEI	480	117.2 (61.8)	87	3 - 229
ACEI/HCTZ	236	86.1 (35.7)	97	7 - 144
ARB/HCTZ	274	66.0 (17.5)	57	7 – 90
Ali/Val/HCTZ	168	54.5 (7.2)	56	1 - 64

- * Duration of exposure to study drug was analyzed cumulatively for patients in both Study CSPP100A 2302 and Study CSPP100A 2302E1.
- ACEI: all lisinopril or ramipril mono treatment groups
- ACEI/HCTZ: all lisinopril/HCTZ or ramipril/HCTZ combination treatment groups.
- ARB/HCTZ: all valsartan/HCTZ or Irbsartan/HCTZ combination treatment groups.
- Patients titrating to several doses within a treatment regimen were counted separately in each (dose) group.

Common adverse events

Placebo-controlled studies

The most frequently observed adverse events (AEs) in the placebo-controlled studies are presented by treatment group in Table 37. Overall, headache and nasopharyngitis were the most frequent AEs. The incidence of headache ranged from 4.6% in the aliskiren/HCTZ 150/6.25 mg group to 13.5% in the placebo group. The incidence of nasopharyngitis ranged from 1.6% in the aliskiren/HCTZ 150/12.5 mg group to 5.4% in the aliskiren/HCTZ 75/25 mg group, compared to 5.2% in the placebo group. Dizziness was one of the more prevalent AEs in the HCTZ 25 mg, aliskiren/HCTZ 150/12.5 mg, and 300/12.5 mg groups, with incidences of 3.5%, 3.3% and 5.0%, respectively. The rate of dizziness was comparable in the combined HCTZ monotherapy group (2.3%) and in the combined aliskiren/HCTZ group (2.3%). Diarrhoea was reported in rates ≥ 2% in the aliskiren/HCTZ 300/12.5 mg, aliskiren/HCTZ 150/25 mg, HCTZ 12.5 mg, and aliskiren 300 mg groups (3.3%, 3.2%, 2.7%, and 2.2%,respectively).

Overall there was no dose dependency seen in AEs among all the aliskiren/HCTZ combination doses included in the studies.

Table 37: Number (%) of patients with most frequent AEs (> = 2% for any treatment group) by preferred term - Group A (short-term double-blind placebo-controlled studies) (safety population)

Preferred term	Placebo N=193 n (%)	Ali 75 mg N=184 n (%)	Ali 150 mg N=185 n (%)	Ali 300 mg N=181 n (%)	Mono Ali N=550 n (%)	HCTZ 6.25 mg N=194 n (%)	HCTZ 12.5 mg N=188 n (%)	HCTZ 25 mg N=173 n (%)	Mono HCTZ N=555 n (%)
Any Adverse Experience	**85(44.0)**	**69(37.5)**	**69(37.3)**	**71(39.2)**	**209(38.0)**	**75(38.7)**	**79(42.0)**	**72(41.6)**	**226(40.7)**
Headache	26(13.5)	13 (7.1)	13 (7.0)	10 (5.5)	36 (6.5)	12 (6.2)	15 (8.0)	12 (6.9)	39 (7.0)
Nasopharyngitis	10 (5.2)	9 (4.9)	5 (2.7)	3 (1.7)	17 (3.1)	6 (3.1)	9 (4.8)	6 (3.5)	21 (3.8)
Dizziness	2 (1.0)	1 (0.5)	1 (0.5)	3 (1.7)	5 (0.9)	4 (2.1)	3 (1.6)	6 (3.5)	13 (2.3)
Influenza	3 (1.6)	1 (0.5)	7 (3.8)	3 (1.7)	11 (2.0)	0 (0.0)	3 (1.6)	3 (1.7)	6 (1.1)
Diarrhoea	1 (0.5)	3 (1.6)	3 (1.6)	4 (2.2)	10 (1.8)	3 (1.5)	5 (2.7)	3 (1.7)	11 (2.0)
Back pain	5 (2.6)	3 (1.6)	4 (2.2)	1 (0.6)	8 (1.5)	1 (0.5)	1 (0.5)	4 (2.3)	6 (1.1)
Cough	1 (0.5)	1 (0.5)	2 (1.1)	1 (0.6)	4 (0.7)	1 (0.5)	1 (0.5)	2 (1.2)	4 (0.7)
Bronchitis	3 (1.6)	1 (0.5)	4 (2.2)	5 (2.8)	10 (1.8)	2 (1.0)	1 (0.5)	1 (0.6)	4 (0.7)
Asthenia	0 (0.0)	3 (1.6)	2 (1.1)	1 (0.6)	6 (1.1)	3 (1.5)	2 (1.1)	1 (0.6)	6 (1.1)
Nausea	4 (2.1)	1 (0.5)	1 (0.5)	2 (1.1)	4 (0.7)	3 (1.5)	3 (1.6)	1 (0.6)	7 (1.3)
Vertigo	1 (0.5)	2 (1.1)	0 (0.0)	1 (0.6)	3 (0.5)	1 (0.5)	4 (2.1)	1 (0.6)	6 (1.1)
Upper respiratory tract infection	2 (1.0)	2 (1.1)	0 (0.0)	5 (2.8)	7 (1.3)	0 (0.0)	2 (1.1)	2 (1.2)	4 (0.7)
Palpitations	3 (1.6)	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.4)	2 (1.0)	4 (2.1)	0 (0.0)	6 (1.1)
Arthralgia	1 (0.5)	4 (2.2)	0 (0.0)	0 (0.0)	4 (0.7)	0 (0.0)	2 (1.1)	1 (0.6)	3 (0.5)
Abdominal pain upper	1 (0.5)	1 (0.5)	1 (0.5)	3 (1.7)	5 (0.9)	3 (1.5)	3 (1.6)	2 (1.2)	8 (1.4)
Oedema peripheral	1 (0.5)	4 (2.2)	3 (1.6)	2 (1.1)	9 (1.6)	2 (1.0)	3 (1.6)	1 (0.6)	6 (1.1)
Constipation	3 (1.6)	4 (2.2)	0 (0.0)	3 (1.7)	7 (1.3)	1 (0.5)	1 (0.5)	1 (0.6)	3 (0.5)
Muscle spasms	1 (0.5)	4 (2.2)	3 (1.6)	3 (1.7)	10 (1.8)	0 (0.0)	2 (1.1)	3 (1.7)	5 (0.9)
Urinary tract infection	3 (1.6)	2 (1.1)	2 (1.1)	1 (0.6)	5 (0.9)	2 (1.0)	1 (0.5)	2 (1.2)	5 (0.9)
Flatulence	1 (0.5)	1 (0.5)	0 (0.0)	2 (1.1)	3 (0.5)	0 (0.0)	2 (1.1)	1 (0.6)	3 (0.5)
Vomiting	4 (2.1)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)	2 (1.0)	0 (0.0)	1 (0.6)	3 (0.5)
Rhinitis	0 (0.0)	1 (0.5)	1 (0.5)	2 (1.1)	4 (0.7)	0 (0.0)	2 (1.1)	4 (2.3)	6 (1.1)

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Preferred term	Ali/HCTZ 75/6.25 mg N=188 n (%)	Ali/HCTZ 75/12.5 mg N=190 n (%)	Ali/HCTZ 75/25 mg N=186 n (%)	Ali/HCTZ 150/6.25 mg N=174 n (%)	Ali/HCTZ 150/12.5 mg N=184 n (%)	Ali/HCTZ 150/25 mg N=188 n (%)	Ali/HCTZ 300/12.5 mg N=181 n (%)	Ali/HCTZ 300/25 mg N=173 n (%)	Ali/HCTZ N=1464 n (%)
Any Adverse Experience	**65(34.6)**	**75(39.5)**	**77(41.4)**	**66(37.9)**	**72(39.1)**	**83(44.1)**	**82(45.3)**	**71(41.0)**	**591(40.4)**
Headache	11 (5.9)	14 (7.4)	11 (5.9)	8 (4.6)	15 (8.2)	9 (4.8)	16 (8.8)	14 (8.1)	98 (6.7)
Nasopharyngitis	9 (4.8)	6 (3.2)	10 (5.4)	5 (2.9)	3 (1.6)	7 (3.7)	7 (3.9)	9 (5.2)	56 (3.8)
Dizziness	1 (0.5)	5 (2.6)	5 (2.7)	2 (1.1)	6 (3.3)	3 (1.6)	9 (5.0)	3 (1.7)	34 (2.3)
Influenza	5 (2.7)	5 (2.6)	4 (2.2)	3 (1.7)	1 (0.5)	6 (3.2)	2 (1.1)	7 (4.0)	33 (2.3)
Diarrhoea	0 (0.0)	2 (1.1)	3 (1.6)	3 (1.7)	1 (0.5)	6 (3.2)	6 (3.3)	3 (1.7)	24 (1.6)
Back pain	2 (1.1)	7 (3.7)	1 (0.5)	1 (0.6)	2 (1.1)	3 (1.6)	3 (1.7)	2 (1.2)	21 (1.4)
Cough	3 (1.6)	3 (1.6)	2 (1.1)	2 (1.1)	2 (1.1)	4 (2.1)	2 (1.1)	1 (0.6)	19 (1.3)
Bronchitis	1 (0.5)	2 (1.1)	2 (1.1)	4 (2.3)	4 (2.2)	2 (1.1)	1 (0.6)	2 (1.2)	18 (1.2)
Asthenia	1 (0.5)	2 (1.1)	4 (2.2)	2 (1.1)	1 (0.5)	3 (1.6)	2 (1.1)	2 (1.2)	17 (1.2)
Nausea	2 (1.1)	5 (2.6)	0 (0.0)	1 (0.6)	2 (1.1)	4 (2.1)	2 (1.1)	1 (0.6)	17 (1.2)
Vertigo	2 (1.1)	2 (1.1)	1 (0.5)	0 (0.0)	1 (0.5)	3 (1.6)	3 (1.7)	5 (2.9)	17 (1.2)
Upper respiratory tract infection	2 (1.1)	0 (0.0)	2 (1.1)	3 (1.7)	3 (1.6)	2 (1.1)	2 (1.1)	2 (1.2)	16 (1.1)
Palpitations	1 (0.5)	2 (1.1)	1 (0.5)	1 (0.6)	2 (1.1)	5 (2.7)	2 (1.1)	1 (0.6)	15 (1.0)
Arthralgia	2 (1.1)	2 (1.1)	6 (3.2)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)	2 (1.2)	14 (1.0)
Abdominal pain upper	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	3 (1.6)	4 (2.1)	1 (0.6)	2 (1.2)	13 (0.9)
Oedema peripheral	1 (0.5)	3 (1.6)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.5)	3 (1.7)	3 (1.7)	13 (0.9)
Constipation	3 (1.6)	2 (1.1)	2 (1.1)	0 (0.0)	1 (0.5)	2 (1.1)	2 (1.1)	0 (0.0)	12 (0.8)
Muscle spasms	3 (1.6)	1 (0.5)	3 (1.6)	1 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.2)	11 (0.8)
Urinary tract infection	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.1)	3 (1.6)	0 (0.0)	5 (2.8)	0 (0.0)	11 (0.8)
Flatulence	1 (0.5)	0 (0.0)	4 (2.2)	1 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)	8 (0.5)
Vomiting	0 (0.0)	1 (0.5)	2 (1.1)	0 (0.0)	3 (1.6)	2 (1.1)	0 (0.0)	0 (0.0)	8 (0.5)
Rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.1)	2 (1.1)	1 (0.6)	6 (0.4)

Short-term controlled studies

The most frequently observed AEs in the short-term controlled studies are presented by treatment group in Table 38. Results were consistent with those in the placebo-controlled studies. AEs experienced by ≥1% of patients taking aliskiren/HCTZ and that occurred more frequently than in patients taking placebo were dizziness, diarrhoea, and arthralgia.

Long-term open-label studies

The most frequently reported AEs in the long-term open-label studies are summarised in Table 39. The most frequently reported AE with aliskiren/HCTZ and aliskiren monotherapy was nasopharyngitis (6.1% and 6.9%, respectively). The incidence of headache was 2.5% in the aliskiren/HCTZ group and 7.8% in the aliskiren monotherapy group. There was no evidence of an increase in AE rates with the addition of HCTZ to aliskiren treatment.

Long-term double-blind studies

The most frequently reported AEs during the long-term double-blind studies are summarised in Table 40. The most frequently reported AEs during long-term double-blind treatment with aliskiren/HCTZ were dizziness, nasopharyngitis, fatigue, and headache. Diarrhoea was reported in more patients treated with aliskiren monotherapy and the combination of aliskiren/HCTZ compared to patients treated with ramipril monotherapy and the combination of ramipril/HCTZ.

Drug-related adverse events

Overall, AEs that were suspected by the investigator to be study drug-related were reported in 12.2% of patients treated aliskiren/HCTZ, 8.8% of patients treated with placebo, 7.8% of patients treated with aliskiren monotherapy, and 10.1% of patients treated with HCTZ monotherapy.

Table 38: Number (%) of patients with most frequent AEs (> = 2% for any group) by preferred term - Group B (short term, double-blind all controlled studies) (safety population)

Preferred term	Placebo N=193 n (%)	Mono Ali N=973 n (%)	Mono HCTZ N=1075 n (%)	Ali/HCTZ 75/6.25 mg N=188 n (%)	Ali/HCTZ 75/12.5 mg N=190 n (%)	Ali/HCTZ 75/25 mg N=186 n (%)	Ali/HCTZ 150/6.25 mg N=174 n (%)	Ali/HCTZ 150/12.5 mg N=184 n (%)
Any adverse experience	**85(44.0)**	**312(32.1)**	**420(39.1)**	**65(34.6)**	**75(39.5)**	**77(41.4)**	**66(37.9)**	**72(39.1)**
Headache	26(13.5)	56(5.8)	61(5.7)	11(5.9)	14(7.4)	11(5.9)	8(4.6)	15(8.2)
Nasopharyngitis	10(5.2)	25(2.6)	42(3.9)	9(4.8)	6(3.2)	10(5.4)	5(2.9)	3(1.6)
Dizziness	2(1.0)	6(0.6)	21(2.0)	1(0.5)	5(2.6)	5(2.7)	2(1.1)	6(3.3)
Influenza	3(1.6)	12(1.2)	9(0.8)	5(2.7)	5(2.6)	4(2.2)	3(1.7)	1(0.5)
Diarrhoea	1(0.5)	14(1.4)	20(1.9)	0(0.0)	2(1.1)	3(1.6)	3(1.7)	1(0.5)
Back pain	5(2.6)	10(1.0)	14(1.3)	2(1.1)	7(3.7)	1(0.5)	1(0.6)	2(1.1)
Arthralgia	1(0.5)	7(0.7)	11(1.0)	2(1.1)	2(1.1)	6(3.2)	0(0.0)	1(0.5)
Bronchitis	3(1.6)	11(1.1)	10(0.9)	1(0.5)	2(1.1)	2(1.1)	4(2.3)	4(2.2)
Cough	1(0.5)	5(0.5)	10(0.9)	3(1.6)	3(1.6)	2(1.1)	2(1.1)	2(1.1)
Vertigo	1(0.5)	6(0.6)	7(0.7)	2(1.1)	2(1.1)	1(0.5)	0(0.0)	1(0.5)
Nausea	4(2.1)	4(0.4)	10(0.9)	2(1.1)	5(2.6)	0(0.0)	1(0.6)	2(1.1)
Asthenia	0(0.0)	8(0.8)	7(0.7)	1(0.5)	2(1.1)	4(2.2)	2(1.1)	1(0.5)
Fatigue	2(1.0)	6(0.6)	13(1.2)	1(0.5)	3(1.6)	1(0.5)	2(1.1)	1(0.5)
Oedema peripheral	1(0.5)	11(1.1)	13(1.2)	1(0.5)	3(1.6)	0(0.0)	0(0.0)	2(1.1)
Sinusitis	1(0.5)	3(0.3)	1(0.1)	0(0.0)	1(0.5)	0(0.0)	1(0.6)	1(0.5)
Vomiting	4 (2.1)	1(0.1)	5(0.5)	0(0.0)	1(0.5)	2(1.1)	0(0.0)	3(1.6)
Flatulence	1 (0.5)	4(0.4)	3(0.3)	1(0.5)	0(0.0)	4(2.2)	1(0.6)	0(0.0)
Angina pectoris	0 (0.0)	1(0.1)	2(0.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Tendonitis	0 (0.0)	4(0.4)	2(0.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Continued on next page.

Preferred term	Ali/HCTZ 150/25 mg N=719 n (%)	Ali/HCTZ 300/12.5 mg N=474 n (%)	Ali/HCTZ 300/25 mg N=1030 n (%)	Ali/HCTZ N=2875 n (%)	Amlodipine/ HCTZ N=127 n (%)	Lisinopril N=58 n (%)	Lisinopril/ HCTZ N=26 n (%)	ARB/HCTZ N=274 n (%)	Ali/Val/HCTZ N=168 n (%)
Any adverse experience	**228(31.7)**	**135(28.5)**	**297(28.8)**	**998(34.7)**	**57(44.9)**	**14(24.1)**	**3(11.5)**	**116(42.3)**	**62(36.9)**
Headache	21(2.9)	22(4.6)	28(2.7)	129(4.5)	9(7.1)	5(8.6)	0(0.0)	12(4.4)	5(3.0)
Nasopharyngitis	22(3.1)	9(1.9)	28(2.7)	92(3.2)	7(5.5)	2(3.4)	0(0.0)	10(3.6)	3(1.8)
Dizziness	10(1.4)	12(2.5)	17(1.7)	58(2.0)	1(0.8)	1(1.7)	1(3.8)	16(5.8)	10(6.0)
Influenza	10(1.4)	4(0.8)	12(1.2)	44(1.5)	0(0.0)	0(0.0)	0(0.0)	2(0.7)	0(0.0)
Diarrhoea	10(1.4)	10(2.1)	8(0.8)	37(1.3)	1(0.8)	0(0.0)	0(0.0)	3(1.1)	2(1.2)
Back pain	6(0.8)	5(1.1)	10(1.0)	34(1.2)	5(3.9)	1(1.7)	0(0.0)	4(1.5)	4(2.4)
Arthralgia	6(0.8)	4(0.8)	7(0.7)	28(1.0)	1(0.8)	0(0.0)	0(0.0)	4(1.5)	0(0.0)
Bronchitis	4(0.6)	4(0.8)	7(0.7)	28(1.0)	2(1.6)	0(0.0)	0(0.0)	5(1.8)	2(1.2)
Cough	7(1.0)	2(0.4)	6(0.6)	27(0.9)	3(2.4)	1(1.7)	0(0.0)	5(1.8)	3(1.8)
Vertigo	4(0.6)	5(1.1)	12(1.2)	27(0.9)	2(1.6)	0(0.0)	0(0.0)	3(1.1)	4(2.4)
Nausea	5(0.7)	3(0.6)	4(0.4)	22(0.8)	1(0.8)	1(1.7)	0(0.0)	4(1.5)	3(1.8)
Asthenia	3(0.4)	3(0.6)	4(0.4)	20(0.7)	2(1.6)	0(0.0)	0(0.0)	2(0.7)	1(0.6)
Fatigue	4(0.6)	2(0.4)	6(0.6)	20(0.7)	1(0.8)	2(3.4)	0(0.0)	5(1.8)	4(2.4)
Oedema peripheral	2(0.3)	3(0.6)	5(0.5)	16(0.6)	14(11.0)	0(0.0)	0(0.0)	2(0.7)	1(0.6)
Sinusitis	4(0.6)	3(0.6)	2(0.2)	12(0.4)	3(2.4)	0(0.0)	0(0.0)	0(0.0)	3(1.8)
Vomiting	4(0.6)	0(0.0)	1(0.1)	11(0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Flatulence	1(0.1)	1(0.2)	2(0.2)	10(0.3)	0(0.0)	0(0.0)	0(0.0)	2(0.7)	0 (0.0)
Angina pectoris	0(0.0)	0(0.0)	2(0.2)	3(0.1)	1(0.8)	0(0.0)	1(3.8)	0(0.0)	0 (0.0)
Myocardial infarction	0(0.0)	0(0.0)	2(0.2)	3(0.1)	0(0.0)	0(0.0)	1(3.8)	0(0.0)	0 (0.0)
Tendonitis	0(0.0)	0(0.0)	3(0.3)	3(0.1)	0(0.0)	0(0.0)	1(3.8)	0(0.0)	0 (0.0)

Table 39: Number (%) of patients with most frequent AEs (> = 2% for any treatment group) by preferred term - Group C (long-term open-label studies) (safety population)

Preferred term	Mono Ali N=1955 n (%)	Ali/HCTZ 300/12.5 mg N=843 n (%)	Ali/HCTZ 300/25 mg N=454 n (%)	Ali/HCTZ N=871 n (%)
Any Adverse Experience	1050 (53.7)	314 (37.2)	197 (43.4)	464 (53.3)
Nasopharyngitis	135 (6.9)	38 (4.5)	15 (3.3)	53 (6.1)
Bronchitis	72(3.7)	19(2.3)	18(4.0)	36(4.1)
Dizziness	75 (3.8)	21 (2.5)	11 (2.4)	31 (3.6)
Back pain	68 (3.5)	22 (2.6)	5 (1.1)	28 (3.2)
Influenza	50 (2.6)	16 (1.9)	10 (2.2)	26 (3.0)
Headache	153 (7.8)	12 (1.4)	10 (2.2)	22 (2.5)
Arthralgia	36 (1.8)	8 (0.9)	11 (2.4)	19 (2.2)
Cough	30 (1.5)	15 (1.8)	4 (0.9)	19 (2.2)
Diarrhoea	69 (3.5)	12 (1.4)	6 (1.3)	18 (2.1)
Upper respiratory tract infection	42 (2.1)	12 (1.4)	4 (0.9)	16 (1.8)
Fatigue	41 (2.1)	10 (1.2)	2 (0.4)	12 (1.4)
Nausea	42 (2.1)	0 (0.0)	5 (1.1)	5 (0.6)

Twenty-eight patients received aliskiren/HCTZ combination treatment other than aliskiren/HCTZ 300/12.5 mg (first titrated combination dose).

Table 40: Number (%) of patients with most frequent AEs (> = 2% for any treatment group) by preferred term - Group D (long-term double-blind studies) (safety population)

Preferred term	Mono Ali N=421 n (%)	Ali/HCTZ 300/12.5 mg N=193 n (%)	Ali/HCTZ 300/25 mg N=92 n (%)	Ali/HCTZ N=193 n (%)	Ramipril N=422 n (%)	Ramipril/ HCTZ/ N=210 n (%)
Any adverse experience	237 (56.3)	64 (33.2)	35 (38.0)	85 (44.0)	234 (55.5)	98 (46.7)
Dizziness	16 (3.8)	7 (3.6)	1 (1.1)	8 (4.1)	16 (3.8)	5 (2.4)
Nasopharyngitis	19 (4.5)	5 (2.6)	3 (3.3)	8 (4.1)	24 (5.7)	9 (4.3)
Fatigue	13 (3.1)	3 (1.6)	3 (3.3)	6 (3.1)	16 (3.8)	1 (0.5)
Headache	45 (10.7)	6 (3.1)	1 (1.1)	6 (3.1)	33 (7.8)	8 (3.8)
Bronchitis	10 (2.4)	5 (2.6)	0 (0.0)	5 (2.6)	5 (1.2)	2 (1.0)
Diarrhoea	13 (3.1)	2 (1.0)	3 (3.3)	5 (2.6)	8 (1.9)	1 (0.5)
Sinusitis	4 (1.0)	4 (2.1)	2 (2.2)	5 (2.6)	8 (1.9)	4 (1.9)
Upper respiratory tract infection	11 (2.6)	3 (1.6)	2 (2.2)	5 (2.6)	11 (2.6)	13 (6.2)
Cough	14 (3.3)	3 (1.6)	0 (0.0)	3 (1.6)	34 (8.1)	9 (4.3)
Pain in extremity	13 (3.1)	2 (1.0)	1 (1.1)	3 (1.6)	5 (1.2)	3 (1.4)
Back pain	13 (3.1)	1 (0.5)	1 (1.1)	2 (1.0)	7 (1.7)	8 (3.8)
Blood glucose increased	0 (0.0)	0 (0.0)	2 (2.2)	2 (1.0)	1 (0.2)	1 (0.5)
Nausea	10 (2.4)	1 (0.5)	1 (1.1)	2 (1.0)	5 (1.2)	3 (1.4)
Oedema peripheral	14 (3.3)	1 (0.5)	1 (1.1)	2 (1.0)	13 (3.1)	2 (1.0)
Dyspepsia	11 (2.6)	0 (0.0)	1 (1.1)	1 (0.5)	4 (0.9)	0 (0.0)

The most frequently affected system organ classes (SOCs) were nervous system disorders, gastrointestinal disorders and general disorders and administration site conditions.

The highest incidence of drug-related AEs involved nervous system disorders, which were reported in 4.2% of patients receiving aliskiren/HCTZ, 4.1% of patients receiving placebo, 1.5% of patients receiving aliskiren monotherapy, and 3.2% of patients receiving HCTZ monotherapy. Headache was generally the most common drug-related AE in the nervous system disorders SOC; reported in 2.3% of aliskiren/HCTZ-treated patients, 4.1% of placebo-treated patients, 0.7% of aliskiren monotherapy-treated patients, and 2.2% of HCTZ monotherapy-treated patients.

Drug-related AEs involving gastrointestinal disorders were reported in 2.8% of patients receiving aliskiren/HCTZ, 1.6% of patients receiving placebo, 1.3% of patients receiving aliskiren monotherapy, and 2.5% of patients receiving HCTZ monotherapy. Among AEs involving gastrointestinal disorders, diarrhoea was reported in 0.1% of aliskiren/HCTZ-treated patients, 0.0% of placebo-treated patients, 0.4% of aliskiren monotherapy-treated patients, and 0.4% of HCTZ monotherapy-treated patients.

There were no reported AEs of angioedema in the aliskiren/HCTZ treated patients. There were no reports of drug-related rash in the aliskiren/HCTZ 150/12.5 mg and 300/25 mg treated patients, and only 1 report (0.6%) in the aliskiren/HCTZ 300/12.5 mg and 2 reports (1.1%) in the aliskiren/HCTZ 150/6.25 mg treated patients.

Results in the short-term controlled studies were consistent with those in the placebo-controlled studies. Overall, AEs that were suspected by the investigator to be drug- related were reported in 9.3% of patients treated with aliskiren/HCTZ, 8.8% of patients treated with placebo, 6.4% of patients treated with aliskiren monotherapy, 8.1% of patients treated with HCTZ monotherapy, 14.2% of patients treated with angiotensin receptor blockers/HCTZ, and 18.1% of patients treated with amlodipine/HCTZ.

In the long-term open-label studies, AEs that were suspected by the investigator to be study drug related were reported in 11.8% of patients treated with aliskiren monotherapy, 8.6% of patients treated with aliskiren/HCTZ overall, 5.9% of patients treated with aliskiren/HCTZ 300/12.5 mg, and 6.6% of patients treated with aliskiren/HCTZ 300/25 mg. Diarrhoea was suspected to be study drug related in 0.8% of patients treated with aliskiren monotherapy, 0.5% of patients treated with aliskiren/HCTZ overall, 0.4% of patients treated with aliskiren/HCTZ 300/12.5 mg, and 0.2% of patients treated with aliskiren/HCTZ 300/25 mg. In the long-term double-blind studies there was no evidence of an increase in adverse event incidence rates that were suspected to be study drug related with addition of HCTZ to aliskiren treatment.

Severity of events

Overall, most AEs were rated by the investigator as mild or moderate in intensity. In the short-term controlled studies and placebo-controlled studies AEs that were rated by the investigator as severe were reported in 2.6% of patients treated with aliskiren/HCTZ, 1.0% of patients treated with placebo, 2.2% of patients treated with aliskiren monotherapy, and 1.6% of patients treated with HCTZ monotherapy. No patient experienced an AE of diarrhoea rated as severe.

Deaths

Overall, 12 deaths occurred during or after completed studies which contained the treatment of aliskiren in combination with HCTZ. Two patients are known to have taken aliskiren/HCTZ at any time, five patients were treated with aliskiren monotherapy, one patient was treated with HCTZ monotherapy, and one patient was treated with valsartan/HCTZ. The causes of death were similar in all groups, and comparable in patients treated with aliskiren/HCTZ and the component monotherapies, active comparators, or placebo.

Serious adverse events

The proportion of patients with any serious adverse event (SAE) was low and generally similar across all treatment groups in the placebo-controlled and short-term controlled trials. In the combined group of all patients who took aliskiren/HCTZ the rate was 1.3% in the placebo-controlled studies and 1.0% in the short-term controlled studies. The proportion of patients experiencing SAEs with aliskiren monotherapy was 0.5% in the placebo-controlled studies and 0.7% in the short-term controlled studies. The proportion of patients experiencing SAEs with HCTZ monotherapy was 1.1% in the placebo-controlled studies and 1.0% in the short-term controlled

studies. In both Group A and Group B populations, for aliskiren/HCTZ, the system organ class with the most SAEs was nervous system disorders (< 0.3%).

In relation to SAEs leading to study drug discontinuation, for the aliskiren/HCTZ group in the placebo-controlled studies, the SOC with the most SAEs leading to study discontinuation was cardiac disorders (0.1%), while in the short-term controlled studies, the SOCs with the most SAEs leading to study discontinuation were cardiac disorders and nervous system disorders (0.1%). The proportion of patients with any SAE leading to study discontinuation was low and generally similar across all treatment groups. For the aliskiren/HCTZ group, in both the long-term open-label and long-term double-blind studies, the SOC with the most SAEs leading to study discontinuation was cardiac disorders (0.5% in both).

Adverse events of special interest

Angioedema

Angioedema is a known serious side effect of ACE inhibitors. There was only one case of angioedema reported in patients who received the combination of aliskiren/HCTZ (in Study CSPP100A2302). This 47-year old female experienced the event on Day 372 of the study. Study drug was not interrupted. She completed the study 4 days later and the event was completely resolved.

Cough

Cough occurred in ≤ 2.1% of patients in any treatment group in the placebo-controlled studies. It was reported in 0.5% of patients receiving placebo, 0.7% of patients receiving aliskiren monotherapy, 0.7% of patients receiving HCTZ monotherapy, and 1.3% of patients receiving aliskiren/HCTZ. Similarly, in the short-term controlled studies cough was reported in 0.5% of patients receiving placebo, 0.5% of patients receiving aliskiren monotherapy, 0.9% of patients receiving HCTZ monotherapy, and 0.9% of patients receiving aliskiren/HCTZ.

In the long-term open-label studies, the incidence of cough was 1.5% for aliskiren monotherapy and 2.2% for aliskiren/HCTZ combination therapy. In the long-term double-blind studies, the incidence of cough was 3.3% for aliskiren monotherapy and 1.6% for aliskiren in combination with HCTZ.

Diarrhoea

Diarrhoea was observed at higher rate in aliskiren/HCTZ (n = 37, 1.3%) compared to placebo (n = 1, 0.5%) in all short-term controlled trials. Diarrhoea is considered as an adverse drug reaction for the aliskiren/HCTZ combination. It is a known dose related adverse reaction for aliskiren. The incidence of diarrhoea was not higher with the aliskiren/HCTZ combination compared to aliskiren (n = 14, 1.4%) or HCTZ (n = 20, 1.9%) alone. This event was usually limited in duration and most often reported as mild to moderate in severity.

Laboratory evaluations

Haematology

A slight decrease from baseline in mean haemoglobin was observed in the aliskiren monotherapy and aliskiren/HCTZ combination treatment groups (0.1 g/dL and 0.5 g/dL, respectively in the short-term controlled studies). Similar results were seen in the long term studies. Decreased haemoglobin is reported in the labels of aliskiren and aliskiren/HCTZ.

Clinical chemistry

For all treatments, most clinical chemistry parameters remained consistent from baseline to endpoint, and any changes were not considered to be clinically significant.

In all short-term controlled trials, a mean increase in creatinine was seen in the aliskiren/HCTZ group (0.39 mmol/L) that was numerically greater compared with the HCTZ group (0.19 mmol/L), but lower than that of the lisinopril/HCTZ (0.52 mmol/L) group. The proportion of patients with > 50% increases in creatinine in the aliskiren/HCTZ group was comparable to the HCTZ monotherapy and other HCTZ containing combination groups. The majority of these increases were not outside the laboratory normal range for creatinine.

The mean increase and percentage of patients with > 50% increase from baseline in serum uric acid were generally greater in treatment groups containing HCTZ except for the amlodipine/HCTZ group. These results were consistent with the known effect of HCTZ on serum uric acid.

Mean changes from baseline in potassium values in the short-term controlled trials showed small mean increases for placebo (0.029 mmol/L) and aliskiren monotherapy (0.052 mmol/L) and small mean decreases for aliskiren/HCTZ (-0.053 mmol/L) and HCTZ (-0.061 mmol/L). Overall, for each of the treatment groups (except lisinopril/HCTZ), few patients (< 3.0%) demonstrated a > 20% decrease in potassium even in the HCTZ treatment group. In the placebo-controlled trials and the short-term controlled trials, the incidence of hyperkalaemia (K+ >5.5 mmol/L) in patients treated with aliskiren/HCTZ was lower than in patients treated with aliskiren monotherapy. The incidence of hypokalaemia (K+ < 3.5 mmol/L) in patients treated with aliskiren/HCTZ was lower than in patients treated with HCTZ monotherapy, suggesting that the opposing effect of aliskiren and HCTZ on serum potassium approximately balanced each other. Laboratory findings in long-term studies were consistent with the results observed in the short-term controlled studies.

ECGs, vital signs, body weight and physical examinations

No post-baseline electrocardiograms (ECGs) were performed in the studies. There were no clinically significant changes from baseline in body weight for any treatments.

Orthostatic blood pressure change was defined as a decrease of ≥ 20 mmHg in SBP or a decrease of ≥ 10 mmHg in DBP when moving from a sitting to standing position. Orthostatic BP changes with aliskiren/HCTZ were infrequent, and similar to baseline as at endpoint. Orthostatic hypotension was reported as an AE in very few patients (0.2%) treated with aliskiren/HCTZ in all short-term controlled trials. The incidence of orthostatic blood pressure changes in the long term studies was similar to that seen in the short-term studies.

Special patient populations

Safety data were analysed for subgroup differences including by baseline renal function, age, gender, diabetes, obese patients, patients in Stage 2 hypertension, and patients with additional cardiovascular risk. Results were not significantly different in any of these subgroup analyses compared to results observed in the overall population.

Overdose, Withdrawal and Rebound

There were no reports of overdose with aliskiren/HCTZ in the clinical trials. The most likely manifestations of overdosage would be hypotension, related to the antihypertensive effect of aliskiren. If symptomatic hypotension should occur, supportive treatment should be initiated.

No withdrawal or rebound effects on efficacy of aliskiren monotherapy have been observed. Study CSPP100A2306 had a 4-week, double-blind, placebo-controlled, randomised withdrawal period after 26 weeks of monotherapy (aliskiren or ramipril) or combination (aliskiren/HCTZ or ramipril/HCTZ). Patients treated with aliskiren with or without HCTZ and then randomised to placebo (withdrawal period) showed a gradual increase in BP towards baseline over 3-4 weeks; however no rebound effect was seen.

Summary of Safety

Overall, the safety profile of aliskiren/HCTZ fixed combination was similar to the safety profiles of aliskiren and HCTZ monotherapy. The incidence of overall AEs as well as individual AEs was similar in aliskiren/HCTZ combination therapy to each component monotherapy. Most AEs seen with aliskiren/HCTZ were not dose dependent, nor related to gender, age, or race.

Diarrhoea, the dose dependent AE seen with aliskiren monotherapy, was observed in aliskiren/HCTZ combination treatment with an incidence similar to that of aliskiren and HCTZ monotherapy. With the exception of dizziness, hypotension and related events were uncommon. Although dizziness occurred in more patients treated with aliskiren/HCTZ than with placebo, the difference was not statistically significant, and the incidence of dizziness was not more in the aliskiren/HCTZ than in HCTZ monotherapy. There was no increased incidence in elderly patients compared to young patients in dizziness or any other events potentially related to low blood pressure.

No significant new adverse events were observed with long-term treatment compared to short-term treatment. Overall, no new significant safety signals appeared in the studies submitted for evaluation.

Clinical Summary and Conclusions

In this submission the sponsor is seeking to register Rasilez HCT and Enviage HCT (as trade names of fixed combination of aliskiren/HCTZ) for the treatment of hypertension. Approval is being sought for the initial treatment of hypertensive patients unlikely to achieve control of blood pressure with a single agent, as well as treatment in patients whose blood pressure is not adequately controlled on monotherapy. It is also proposed that Rasilez HCT and Enviage HCT be indicated for treatment of hypertension as replacement therapy in patients already receiving aliskiren and hydrochlorothiazide from separate tablets at the same dose levels.

Overall, the clinical programme included nine clinical studies that enrolled a total of 8,472 treated patients. ***Study CSPP100A2204*** provided the dose response data. It is also the main study that supports the initial therapy indication. ***Study CSPP100A2332*** provided pivotal efficacy data to support the use of aliskiren/HCTZ in patients not adequately responding to aliskiren monotherapy. ***Study CSPP100A2333*** provided pivotal efficacy data and ***Study CSPP100A2331*** and ***Study CSPP100A2309*** provided supportive efficacy data for the use of aliskiren/HCTZ in patients not adequately responding to HCTZ monotherapy.

Study CSPP100A2302 and ***Study CSPP100A2306*** allowed optional add on of HCTZ to aliskiren, and therefore provided supportive efficacy data for the long term use of the aliskiren/HCTZ combination. ***Study CSPP100A2303***, which was conducted in severe hypertensive patients and allowed optional add on of HCTZ to aliskiren, therefore provided efficacy data of the aliskiren regimen (including the combination with HCTZ) in the treatment of severe hypertensive patients.

Study CSPP100A2302 provided data in support of long term efficacy and safety. A 4-month extension to the 12- month study for patients who had already completed at least 8 months of combination therapy with aliskiren/HCTZ 300/25 mg was also conducted: ***Study CSPP100A2302E1***.

Patients with severe or secondary hypertension were excluded in all studies except for study CSPP100A2303, in which the patient population had severe hypertension.

The efficacy data submitted for evaluation have demonstrated the superior efficacy of the combination of aliskiren/HCTZ over placebo in the treatment of hypertension. The majority of the studies assessed efficacy when used in patients who had failed to respond to monotherapy with aliskiren or HCTZ alone.

Results from Study CSPP100A2204, in the general hypertensive population, showed that the combination of aliskiren/HCTZ provided effective diastolic and systolic blood pressure lowering effects compared to aliskiren and HCTZ administered as monotherapy in patients with essential hypertension. Efficacy of all of the combination doses proposed for registration (150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg) was demonstrated.

Study CSPP100A2303 was the only study conducted specifically in patients with severe hypertension. The aliskiren based regimen (with optional addition of HCTZ) produced clinically significant reductions in both diastolic and systolic blood pressure in patients with severe hypertension in the study; however results indicated that lisinopril may be more effective than aliskiren in this population.

The combination of aliskiren/HCTZ provided long-term efficacy with persistent blood pressure reduction over 12 months of treatment of hypertension (Study CSPP100A2302 and Study CSPP100A2302E1). The persistence of effect of aliskiren/HCTZ was demonstrated in patients who remained on the aliskiren/HCTZ combination compared with those who discontinued the treatment (Study CSPP100A2306).

The combination of aliskiren/HCTZ produced clinically and statistically significant additional reductions in both diastolic and systolic blood pressure and additional blood pressure control and response in patients with essential hypertension not adequately responsive to aliskiren 300 mg monotherapy (Study CSPP100A2332)

The combination of aliskiren/HCTZ produced clinically and statistically significant additional reductions in both diastolic and systolic blood pressure and additional blood pressure control and response in patients with essential hypertension not adequately responsive to HCTZ 25 mg monotherapy (Study CSPP100A2333 and Study CSP100A2331).

Only one study enrolled patients who were treated with antihypertensives as combination therapy ***and*** as initial therapy (Study CSPP100A2204). In initial therapy, when used in patients with Stage 2 hypertension, the combination of aliskiren/HCTZ produced greater diastolic and systolic blood pressure reductions and better response rates than each of the respective monotherapies (Study CSPP100A2204) on some parameters. Notably the aliskiren/HCTZ 150/25 mg dose was not shown to be superior to HCTZ 25 mg alone.

Importantly, in Stage 2 patients with additional CV risk, a subanalysis using a BP control goal of <130/80 mmHg was performed. Several of the results did not establish that combination therapy with aliskiren/HCTZ was statistically significantly superior to monotherapy. In particular:

- aliskiren/HCTZ 150/12.5 mg was not superior to aliskiren 150 mg alone
- aliskiren/HCTZ 150/25 mg was not superior to aliskiren 150 mg alone
- aliskiren/HCTZ 300/12.5 mg was not superior to aliskiren 300 mg alone
- aliskiren/HCTZ 300/12.5 mg was not superior to HCTZ 12.5 mg alone
- aliskiren/HCTZ 300/12.5 mg was not superior to placebo
- aliskiren/HCTZ 300/25 mg was not superior to aliskiren 300 mg alone.

The results in relation to use of combination therapy in these patients do not support that combination therapy should be used first line. In patients with additional CV risks, a more aggressive blood pressure control (msSBP <130 mmHg and msDBP <80 mmHg) was assessed. For msDBP the combinations of aliskiren/HCTZ 150/12.5mg and 300/12.5mg demonstrated significant superiority over aliskiren monotherapy, but not HCTZ monotherapy. The combinations of

aliskiren/HCTZ 150/25mg and 300/25mg demonstrated significant superiority to both component monotherapies.

The data were insufficient to support a positive risk benefit balance for the proposed first line indication of the combination medicinal product. In the clinical programme the target population of the proposed first line indication was not sufficiently represented. The results in the small subgroup of hypertensive patients with severe hypertension do not provide sufficient evidence of substantial benefit of aliskiren/HCTZ combination therapy over monotherapy treatments.

Only limited data were submitted for the first line indication of aliskiren/HCTZ in patients with severe hypertension unlikely to be controlled with a single agent. Therefore, it is considered that the use of aliskiren/HCTZ combination should only be approved for the second line indications, i.e. in patients whose blood pressure is not controlled with aliskiren or hydrochlorothiazide monotherapy and for replacement therapy in patients adequately controlled with aliskiren and hydrochlorothiazide.

Overall, the safety profile of the aliskiren/HCTZ fixed combination was similar to the safety profile of aliskiren and HCTZ monotherapy. The incidence of overall AEs as well as individual AEs was similar in aliskiren/HCTZ combination therapy to each component monotherapy. Most AEs seen with aliskiren/HCTZ were not dose dependent, nor related to gender, age, or race.

In relation to the first line indication, guideline CPMP/EWP/238/95 Rev. 2 is relevant. The data have not adequately and consistently demonstrated that the combination of aliskiren/HCTZ has a significant efficacy or safety benefit over monotherapies. The data do support that combination therapy is appropriate in patients whose blood pressure cannot be adequately controlled by a single agent, or as replacement therapy in patients already receiving aliskiren and HCTZ from separate tablets ie a second line indication.

Efficacy results when the combination was administered as initial therapy in patients with markedly elevated blood pressure and additional CV risk do not adequately support first line use of the combination. The support for efficacy is considered insufficient because:

- Only one study enrolled patients who were treated with antihypertensives as combination therapy and as initial therapy
- In initial therapy:
  -When used as initial therapy in patients with Stage 2 hypertension, for several doses the combination of aliskiren/HCTZ, produced significantly greater diastolic and systolic blood pressure reductions and response rates than each of the respective monotherapies; however, notably the aliskiren/HCTZ 150/25 mg dose was not shown to be superior to HCTZ 25 mg alone (p =0.0956; M5, v175, p621)
- In Stage 2 patients with additional CV risk, a subanalysis using a BP control goal of <130/80 mmHg was performed. Several of the results did not establish that combination therapy with aliskiren/HCTZ was statistically significantly superior to monotherapy. In particular:

- aliskiren/HCTZ 150/12.5 mg was not superior to aliskiren 150 mg alone
- aliskiren/HCTZ 150/25 mg was not superior to aliskiren 150 mg alone
- aliskiren/HCTZ 300/12.5 mg was not superior to aliskiren 300 mg alone
- aliskiren/HCTZ 300/12.5 mg was not superior to HCTZ 12.5 mg alone
- aliskiren/HCTZ 300/12.5 mg was not superior to placebo
- aliskiren/HCTZ 300/25 mg was not superior to aliskiren 300 mg alone

- Results for the percentage of patients achieving control of blood pressure measured by msDBP showed that the combinations of aliskiren/HCTZ 150/12.5mg and 300/12.5mg were significantly superior to aliskiren monotherapy, but not HCTZ monotherapy.

In the studies submitted for evaluation no data in relation to mortality and morbidity have been provided. It is therefore not possible to assess whether the combination of aliskiren/HCTZ therapy has any advantage over monotherapy treatment in this regard.

It is recommended that:

1) The application to register Rasilez HCT and Enviage HCT for treatment of hypertension in patients whose blood pressure is not adequately controlled on monotherapy, and as replacement therapy in patients already receiving aliskiren and hydrochlorothiazide from separate tablets at the same dose levels should be approved.

2) The indication for use of Rasilez HCT and Enviage HCT as initial treatment of hypertensive patients unlikely to achieve control of blood pressure with a single agent should NOT be approved**.**

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Approval was recommended from a chemistry, quality control and bioavailability aspect. The application was presented to the 128th meeting (2009/5) of the PSC which issued a supportive recommendation. The PSC endorsed all questions raised by the TGA and in particular the question raised in relation to the reported haemolysis in a number of the subject plasma samples. The PSC had no objections to approval of these products provided all issues were addressed to the satisfaction of the TGA. The quality evaluator states that this is the case. In relation to the haemolysis, the number of instances was such that they did not affect the conclusions of the studies. In its pre-ADEC response the sponsor is requested to provide commentary on this issue, addressing the cause of the haemolysis, in what sorts of samples and at what rate did it occur

Four bioavailability studies were included in the submission together with a justification for not providing bioavailability data in relation to the 150/12.5 fixed-dose combination tablet. The relevant bioequivalence criteria were satisfied in the four studies except in relation to C_{max} for aliskiren in the study comparing the PK profiles of aliskiren and hydrochlorothiazide from the proposed 300/12.5 mg fixed-dose combination tablet with those of the separate monotherapies. The 95% CI for the relevant C_{max} ratio was [0.75 – 1.04] with the lower limit falling just below the recommended 0.8. The Delegate did not view this as having any clinical significance. The justification for not providing some data met the relevant TGA guidelines.

Food does not affect the bioavailability of hydrochlorothiazide from the fixed-dose combination tablets but it reduces the bioavailability of aliskiren. There is a 60% decrease in AUC and an 80% reduction in C_{max}. These changes are similar to those for the monotherapy tablets. The Delegate has made some recommendations for amendments to the PI in relation to this issue. The sponsor has been asked to provide comment and the ADEC has been asked for its opinion on the matter also.

No data was included in this submission in relation to whether there are any PK interactions between aliskiren and hydrochlorothiazide. The sponsor justified this by referring to data provided

in the submission to register the aliskiren monotherapy tablets. This indicated no change to the AUC values but lowering of the C_{max} values (to 78% of the aliskiren monotherapy C_{max} and to 74% of the hydrochlorothiazide C_{max}). The Delegate is satisfied that there is no significant PK interaction between the components of the fixed-dose combination tablets.

Nonclinical

There are no non-clinical objections to the registration of the proposed two new strengths in combination.

The non-clinical data dossier was limited to a number of analytical methods/validation assays and two repeat dose toxicity studies in rats utilising various doses of combined aliskiren and hydrochlorothiazide. These combinations were generally in the ratio of about 12:1, which was the same as that in the highest proposed clinical dose combination of aliskiren 300 mg & hydrochlorothiazide 25 mg (300:25 = 12:1).

The toxicity findings in rats at the maximum tolerated dose (MTD) of the combined formulation of aliskiren and hydrochlorothiazide (150/12 mg) were equivalent to the individual toxicities of aliskiren (150 mg/kg) and hydrochlorothiazide (12 mg/kg). There were no apparent additive or synergistic effects on toxicity with the combined formulations in this single species. However, the exposure margins based on plasma AUC were less than that expected clinically for aliskiren and 1- to 7-fold for hydrochlorothiazide. Higher doses led to unacceptable moribundity in rats.

Compared to monotherapy, plasma toxicokinetic analysis in rats indicated that when used as a combined formulation (150/12 mg/kg), hydrochlorothiazide reduced aliskiren plasma C_{max} and AUC values, whereas aliskiren increased hydrochlorothiazide plasma C_{max} and AUC values. These findings were consistent for hydrochlorothiazide but not for aliskiren in a clinical trial utilizing the 300/25 mg formulation. The mechanism for this pharmacokinetic interaction was not further addressed by the sponsor.

There were no non-clinical data that explicitly assessed the potential genotoxicity, carcinogenicity or reproductive toxicity of combined aliskiren/hydrochlorothiazide.

The conclusions and recommendations of the non-clinical evaluation were as follows:

A very limited non-clinical data dossier was submitted in support of the fixed combination product of aliskiren and hydrochlorothiazide.

There were no findings in the non-clinical data which would preclude, on safety grounds, the registration of the combination for the treatment of hypertension. This recommendation is consistent with EU guidelines for fixed-dose combination products but assumes that there are sufficient clinical safety data which would negate the need for more comprehensive non-clinical data.

Clinical

Pharmacokinetics

No new pharmacokinetic data were presented for evaluation. Since some of the efficacy and safety studies were conducted with the free combination of aliskiren and hydrochlorothiazide, a bioequivalence development programme was included to bridge the clinical efficacy and safety data obtained with the free combination drugs to that for the fixed-dose combination final market image (FMI) tablets. There were three bioequivalence studies. The rate and extent of absorption of aliskiren and hydrochlorothiazide were similar following single oral administration of the fixed combination FMI film-coated tablets containing the following dosage strength combinations: aliskiren 150 mg & hydrochlorothiazide 25 mg, aliskiren 300 mg & hydrochlorothiazide 12.5 mg, aliskiren 300 mg & hydrochlorothiazide 25 mg AND the separate components taken individually at the same respective dosage strengths. For the remaining dosage strength combination, namely

aliskiren 150 mg & hydrochlorothiazide 12.5 mg, the sponsor submitted a justification for not doing the appropriate bioequivalence study. This justification met the requirements of both the TGA and the CHMP, given the composition proportionality and similar manufacturing processes for the fixed-dose combination tablets and the comparable dissolution results across the dosage strength range.

The food-effect study demonstrated that the effect of food on the pharmacokinetics of aliskiren and hydrochlorothiazide are not different when administered as separate monotherapies or as aliskiren/hydrochlorothiazide fixed combination FMI tablets.

Efficacy in Hypertension

Study **CSPP100A-2204**, was a 4 x 4, multifactorial design study which studied all possible combination pairs of aliskiren 0, 75, 150 or 300 mg once daily and hydrochlorothiazide 0, 6.25, 12.5 or 25 mg once daily, except for the combination of aliskiren/hydrochlorothiazide 300/6.25 mg. Thus there were 15 treatment groups (4 x 4 – 1 = 16 -1 = 15). It was nominated as the pivotal study to evaluate the efficacy and safety of the aliskiren/hydrochlorothiazide combination as initial therapy for the treatment of hypertension in patients with Stage 2 (WHO) hypertension and patients with additional CV risk.

Table 41 defines the various grades (stages) of hypertension according to the WHO definition and also provides a CV risk classification (original table is Table 2 on p. 1985 of the article by Prof. Judith Whitworth[6]):

Table 41: Stratification of risk to quantify prognosis

	Blood pressure (mmHg)		
Other risk factors and disease history	Grade 1 (SBP 140–159 or DBP 90–99)	Grade 2 (SBP 160–179 or DBP 100–109)	Grade 3 (SBP ≥ 180 or DBP ≥ 110)
I No other risk factors	Low risk	Medium risk	High risk
II 1–2 risk factors	Medium risk	Medium risk	High risk
III 3 or more risk factors, or TOD, or ACC	High risk	High risk	High risk

SBP, systolic blood pressure; DBP, diastolic blood pressure; TOD, target-organ damage; ACC, associated clinical conditions.

It should be noted that in this study, those with grade 3 (WHO) hypertension were excluded from the study. Patients with grade 2 (WHO) hypertension in this study were thus those either with a systolic BP of between 160 and 179 mm Hg or a diastolic BP of between 100 and 109 mm Hg.

The primary efficacy variable was the change from baseline in mean sitting diastolic blood pressure (msDBP) at endpoint and the main secondary efficacy variable was that for mean sitting systolic blood pressure (msSBP). Tabular summaries of these results are shown in Tables 4 and 5. A helpful reduction of these results is shown in the two tables below, taken from the EMEA Assessment Report for Rasilez HCT[7]:

[6] Whitworth, J.A. (WHO, ISH Writing Group), 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension, *J Hypertens* 2003 Nov; 21(11): 1983-92.

[7] p. 29 of Assessment Report for RASILEZ HCT, Doc. Ref.: EMEA/CHMP/575457/2008

Aliskiren combinations with HCTZ 12.5 mg – placebo-subtracted and HCTZ-subtracted effects on DBP and SBP (primary ITT population – Study CSPP100A2204)

Aliskiren/HCTZ dose (mg)	DBP – PBO-subtracted	SBP – PBO-subtracted	DBP – HCTZ-subtracted	SBP – HCTZ-subtracted
75/12.5	-4.21	-8.16	-1.03	-1.71
150/12.5	-4.97	-10.13	-1.79	-3.69
300/12.5	-6.93	-12.33	-3.76	-5.89

Aliskiren combinations with HCTZ 25 mg – placebo-subtracted and HCTZ-subtracted effects on DBP and SBP (primary ITT population – Study CSPP100A2204)

Aliskiren/HCTZ dose (mg)	DBP – PBO-subtracted	SBP – PBO-subtracted	DBP – HCTZ-subtracted	SBP – HCTZ-subtracted
75/25	-4.52	-9.84	-2.09	-3.02
150/25	-5.71	-11.99	-3.28	-5.17
300/25	-7.33	-13.74	-4.90	-6.92

One can observe an overall pattern of dose-related effect. For the primary diastolic endpoint, most combination doses were statistically superior to their component monotherapies with the exceptions of aliskiren/hydrochlorothiazide 150/6.25 mg vs. each of the two components and aliskiren/hydrochlorothiazide 75/12.5 mg to hydrochlorothiazide 12.5 mg.

The responder rate analysis is shown in Table 6. Generally, for the four proposed dosage strength combinations, the responder rates were significantly better than those for the respective monotherapies or placebo, the only exception being that the responder rate for the aliskiren/hydrochlorothiazide 150/12.5 mg combination was not superior to that for hydrochlorothiazide 12.5 mg alone. With regard to dose-response, one can see a reasonably clear separation between the bottom four rows of the table (corresponding to the combinations which are the subject of this application) and the rows above the bottom four. The one exception is the row corresponding to the combination aliskiren/hydrochlorothiazide 75/25 (although one could argue that this is probably being driven by the effect of hydrochlorothiazide 25 mg).

Analyses relevant to the initial therapy indication for the aliskiren/hydrochlorothiazide combinations

The sponsor performed *post hoc* analyses to support the initial therapy indication. These additional efficacy analyses were performed exclusively for Study CSPP100A-2204, which was the only study in which all patients randomised to the combination groups received the combination of aliskiren/hydrochlorothiazide as the initial treatment without titration from monotherapy.

Two sub-groups were formed for this analysis: patients with Stage 2 hypertension (defined earlier) and patients with additional CV risk, the latter group being defined as those with any of diabetes, renal impairment/decreased GFR (< 90 mL/min/1.73 m^2 at study baseline) or history of CV disease, regardless of the baseline BP level. Out of the total of 1459 patients treated with a Rasilez HCT combination in Study CSPP100A-2204, there were 776 categorized as having Stage 2 hypertension.

The supplemental statistical analyses for patients with Stage 2 hypertension confirmed that all aliskiren/hydrochlorothiazide combination dosage strengths proposed for registration demonstrated statistically significantly greater msDBP and msSBP reductions than the respective monotherapies. These results, shown in Tables 9 and 10, reflect the dose-related effects already observed for the primary endpoint.

Although the overall control rate was relatively low as one would expect in this patient population, all dosage strengths of the aliskiren/hydrochlorothiazide combination proposed for registration demonstrated statistically significantly better blood pressure control rates than those observed for the component monotherapies (Table 11).

The clinical evaluator also made the comment that supplemental analyses for individual SBP control (< 140 mm Hg) rate and individual DBP control (< 90 mm Hg) rate showed that overall a greater number of patients achieved BP control with combination therapy when compared with the respective monotherapies. However, a notable exception was the aliskiren/hydrochlorothiazide 150/25 mg dose which was not superior to hydrochlorothiazide 25 mg alone (p = 0.0956). This result would appear to be at variance with the corresponding result in the table immediately above. The sponsor was requested to clarify this discrepancy in is its pre-ADEC response. Similar results were observed for the sub-group of patients with additional CV risk (Tables 12 to 15).

Study **CSPP100A-2332** was an 8-week, randomized, double-blind, parallel-group, multicentre with 3 treatment groups: aliskiren 300 mg, aliskiren/hydrochlorothiazide 300/25 mg and aliskiren/hydrochlorothiazide 300/12.5 mg (following a 4-day washout and a 4-week single-blind run-in with aliskiren 300 mg monotherapy). In this study with patients not adequately responsive to aliskiren monotherapy, both aliskiren/hydrochlorothiazide 300/25 & 300/12.5 mg groups showed a statistically significantly greater msDBP reduction than the aliskiren 300 mg monotherapy group (ITT) (Table 16).

Both aliskiren/hydrochlorothiazide 300/25 & 300/12.5 mg groups showed statistically significantly greater response and control rates than the aliskiren 300 mg monotherapy group (ITT) (Tables 18 and 19).

Study **CSPP100A-2333** was an 8-week, randomized, double-blind, parallel-group, multicentre study comparing the efficacy and safety of the combination therapies, aliskiren/hydrochlorothiazide 300/25 & 150/25 mg, to hydrochlorothiazide 25 mg monotherapy, in patients with essential hypertension who did not adequately respond to hydrochlorothiazide monotherapy. Both aliskiren/hydrochlorothiazide 300/25 & 150/25 mg combination therapies showed a statistically significantly greater msDBP reduction than the hydrochlorothiazide 25 mg monotherapy group (ITT) (Table 20).

Both aliskiren/hydrochlorothiazide 300/25 & 150/25 mg groups showed statistically significantly greater response and control rates than the hydrochlorothiazide 25 mg monotherapy group (ITT) (Tables 22 and 23).

Study **CSPP100A-2331** was an 8-week, randomized, double-blind, parallel-group, multicentre, active-controlled, dose-escalation study in hypertensive patients who did not adequately respond to hydrochlorothiazide monotherapy (12.5 mg for one week followed by 25 mg for three weeks in the 4-week single-blind run-in). There were four treatment groups in the 8-week double-blind phase: hydrochlorothiazide 25 mg monotherapy, aliskiren/hydrochlorothiazide (150/25 mg for 4 weeks and 300/25 mg for the remaining 4 weeks), valsartan/hydrochlorothiazide and a triple combination of aliskiren/valsartan/hydrochlorothiazide.

In this study in patients not adequately responsive to hydrochlorothiazide monotherapy, aliskiren/hydrochlorothiazide 300/25 mg produced statistically significantly superior reductions in msDBP and msSBP compared to hydrochlorothiazide 25 mg monotherapy (Tables 24, 25).

The aliskiren/hydrochlorothiazide 300/25 mg group showed statistically significantly greater response and control rates (Table 26) than the hydrochlorothiazide 25 mg monotherapy group (ITT).

Study **CSPP100A-2309** was a 12-week, randomised, double-blind, parallel-group study to evaluate the efficacy and safety of the combination aliskiren/hydrochlorothiazide compared to irbesartan or amlodipine with hydrochlorothiazide 25 mg or hydrochlorothiazide 25 mg alone in hypertensive patients with BMI $\geq$ 30 kg/m^2 who did not adequately respond to hydrochlorothiazide 25 mg alone. The combination therapy aliskiren/hydrochlorothiazide 300/25 mg produced statistically

significantly superior reductions in msDBP and msSBP compared to hydrochlorothiazide 25 mg alone (Tables 27, 28).

The response rate for the aliskiren/hydrochlorothiazide 300/25 mg combination therapy was statistically superior compared with that for hydrochlorothiazide 25 mg monotherapy [73.5% vs. 59.0%, p = 0.0193].

Study **CSPP100A-2303** was an 8-week, randomised, double-blind, parallel-group, multicentre study to evaluate the safety and efficacy of aliskiren with optional addition of hydrochlorothiazide compared to lisinopril with the optional addition of hydrochlorothiazide in patients with uncomplicated severe hypertension (105 mm Hg ≤ msDBP ≤ 120 mm Hg). While the results for both treatment regimens were generally comparable, these results have little direct relevance to this application. It cannot inform the debate concerning the use of the combination aliskiren/hydrochlorothiazide as initial treatment for severe hypertension because the initial treatment used in this study was a monotherapy. The main aim of this study was the assessment of aliskiren efficacy in comparison with that of lisinopril.

Study **CSPP100A-2302** was an open-label, multicentre, randomized, parallel-group, dose escalation study of aliskiren 150 mg and 300 mg administered as monotherapy and aliskiren 300 mg administered with hydrochlorothiazide 12.5 mg or 25 mg as needed for BP control in patients with uncomplicated essential hypertension. The study comprised three periods, the third of which involved up to 52 weeks of open-label treatment. Both the combination therapy and monotherapy regimens produced reductions in msDBP and msSBP from baseline and the BP lowering effect was maintained throughout the whole study duration (Table 31). As noted by the clinical evaluator, in this study there were no direct comparisons made between the aliskiren monotherapy group and the aliskiren/hydrochlorothiazide combination therapy group.

Study **CSPP100A-2302E1** involved a 4-month, open-label extension period for a subset of patients at selected centres who completed at least 8 months of open-label combination therapy with aliskiren 300 mg and hydrochlorothiazide 25 mg in the CSPP100A-2302 core study. The main purpose of this study was to obtain 12-month safety data in patients receiving the combination of aliskiren/hydrochlorothiazide 300/25 mg. It was shown that BP reductions were generally maintained during the 4 months of the extension after being treated with at least 8 months of aliskiren/hydrochlorothiazide 300/25 mg.

Study **CSPP100A2306** was a 26-week, randomized, double-blind, multicentre, parallel-group study comparing aliskiren to ramipril in patients with mild to moderate hypertension. The addition of hydrochlorothiazide was permitted in patients whose blood pressure was not adequately controlled (BP ≥ 140/90 mm Hg) after at least 12 weeks of monotherapy treatment if they were receiving aliskiren 300 mg or ramipril 10 mg. Both aliskiren and ramipril treatment regimens, with and without add-on hydrochlorothiazide, produced clinically meaningful reductions from baseline in msDBP and msSBP.

The clinical evaluator was of the opinion that the data submitted for evaluation are sufficient to support the use of aliskiren/hydrochlorothiazide for the treatment of hypertension in patients whose blood pressure is not adequately controlled on monotherapy and as replacement therapy in patients already receiving aliskiren and hydrochlorothiazide from separate tablets at the same individual dose levels. On the other hand, the clinical evaluator was of the opinion that the results of the studies did not adequately support the use of aliskiren/hydrochlorothiazide as initial therapy. The principal reason was that in the clinical programme, there were not substantial numbers of patients enrolled in studies to support the proposed first line indication. Most clinical studies excluded patients with severe hypertension (grade 3 WHO hypertension), poorly controlled diabetes, significant cardiovascular disease, cerebrovascular disease or renal impairment.

Safety

The sponsor presented safety data from all studies. Overall, 8472 patients were included in the aliskiren/hydrochlorothiazide clinical development programme, with 3939 being exposed to aliskiren in combination with hydrochlorothiazide.

The most frequently observed adverse events in the placebo-controlled studies are presented by treatment group in Table 37. Overall, headache and nasopharyngitis were the most frequent AEs. Rates of dizziness were comparable in the combined hydrochlorothiazide monotherapy groups and in the combined aliskiren/hydrochlorothiazide groups (both 2.3%). Diarrhoea was reported at rates above 2% in both combined therapy and monotherapy groups. Overall, there was no obvious pattern of dose dependency for any AE among all the combination aliskiren/hydrochlorothiazide groups.

Adverse events that were suspected by the investigator to be study drug related were reported in 12.2% of patients treated with aliskiren/hydrochlorothiazide, 8.8% of patients treated with placebo, 7.8% patients treated with aliskiren monotherapy and 10.1% of patients treated with hydrochlorothiazide monotherapy. The most frequently affected system organ classes were nervous system disorders (headache), gastrointestinal disorders, general disorders and administration site conditions. Diarrhoea, the dose-dependent AE seen with aliskiren monotherapy, was observed in aliskiren/hydrochlorothiazide combination treatment with an incidence similar to that of the monotherapies.

Most AEs were rated by the investigator as mild or moderate in intensity. There were a total of 12 deaths which occurred during or after completed studies with the combination therapy. The causes of death were similar in all groups and comparable between the groups treated with combination therapy and those with the component monotherapies, active comparators or placebo. The proportions of patients with any serious AE were low and similar across all treatment groups in the placebo-controlled studies, likewise the proportions of patients with serious AE leading to study discontinuation.

AEs of special interest were angioedema (1 case in the combination therapy groups), cough (occurred in ≤ 2.1% of patients in any treatment group in the placebo-controlled studies) and diarrhoea.

No significant new adverse events were observed with long-term treatment compared to short-term treatment. Overall, no new significant safety signals appeared in the studies submitted for evaluation.

Summary of evaluation recommendation

Study CSPP100A-2204, the pivotal study, is relevant for the combination therapy of aliskiren/hydrochlorothiazide as it gives useful dose-finding and efficacy data. It was a placebo-controlled, multifactorial study and its results indicated that both components of the combination therapy significantly contributed to the effects of that combination therapy. The greatest least squares mean reduction of msDBP was seen with the particular combination aliskiren/hydrochlorothiazide 300/25 mg. Pairwise comparisons showed that all combinations proposed for registration, i.e. aliskiren/hydrochlorothiazide 150/12.5 mg, 150/25 mg, 300/12.5 mg & 300/25 mg demonstrated statistically significantly greater msDBP & msSBP reductions than their respective component monotherapies and placebo. With the exception of the pairwise comparison between aliskiren/hydrochlorothiazide 150/12.5 mg and hydrochlorothiazide 12.5 mg, all other pairwise comparisons demonstrated a statistically significantly greater % of responders re msDBP when each combination therapy was compared with each of its component monotherapies and placebo. With regard to the parameter of the % of patients achieving BP control at study end, each combination therapy demonstrated statistically significantly greater improvements across the board

compared with component monotherapies and placebo. In addition, there were a number of supportive studies performed in populations of patients whose blood pressure could not be normalized with either of the component monotherapies. Each of these add-on therapy studies gave positive results. Thus the data submitted for evaluation are sufficient to support the use of aliskiren/hydrochlorothiazide for the treatment of hypertension in patients whose blood pressure is not adequately controlled on monotherapy and as replacement therapy in patients already receiving aliskiren and hydrochlorothiazide from separate tablets at the same individual dose levels.

Only one study, CSPP100A-2204, enrolled patients who were treated with anti-hypertensives as combination therapy and as initial therapy. In initial therapy, when used in patients with Stage 2 hypertension, the combination of aliskiren/hydrochlorothiazide produced greater diastolic and systolic blood pressure reductions and better BP control rates than each of the respective monotherapies. Supplemental analyses of individual SBP & DBP control rates demonstrated that the aliskiren/hydrochlorothiazide 150/25 mg combination was not shown to be superior to hydrochlorothiazide 25 mg alone (the sponsor has been asked to clarify this result). In the clinical programme, there were not substantial numbers of patients enrolled in studies to support the proposed first line indication. Most clinical studies excluded patients with severe hypertension (grade 3 WHO hypertension), poorly controlled diabetes, significant cardiovascular disease, cerebrovascular disease or renal impairment. For these reasons the clinical evaluator recommended rejection of the application for use as initial treatment in hypertensive patients unlikely to achieve control of blood pressure with a single agent.

Overall, the safety profile of the aliskiren/hydrochlorothiazide fixed-dose combination was similar to the safety profile of aliskiren and hydrochlorothiazide monotherapies. There was sufficient long-term exposure in the clinical studies to satisfy the relevant guideline.

Response to the TGA Clinical Evaluation Report by the Sponsor

The sponsor submitted a response to the clinical evaluation report, subtitled an expert statement on first line therapy for treatment of stage 2 hypertension. This response did not provide any new clinical data. Rather it provided arguments in relation to the deficiencies identified in the evaluation report. These arguments were principally in relation to Study CSPP100A-2204 which was acknowledged by the sponsor as the pivotal trial to support the initial therapy indication for Rasilez HCT and Enviage HCT. There were firstly arguments aimed at demonstrating the validity of the pivotal multifactorial study 2204 and the *post hoc* analyses conducted by the sponsor in stage 2 hypertensive patients to support the first line indication. There was a re-presentation of the efficacy data from study 2204. Next was a re-presentation of the data which demonstrated early onset and maintenance of greater BP reduction and control with aliskiren/hydrochlorothiazide combination therapies over monotherapies. Finally, there was a summary of the safety profile of the fixed-dose combination, particularly in relation to use in patients with stage 2 hypertension. What evidence there is does seem to suggest that the safety profile of the aliskiren/hydrochlorothiazide combination in patients with stage 2 hypertension is not different from that observed in the general population of hypertensive patients or in patients with stage 1 hypertension.

Based on the TGA evaluation, the sponsor decided to revise the wording of the first line indication to refine the target population of patients with stage 2 hypertension. The revised wording of the proposed first line indication is as follows:

TRADENAME is indicated for the initial treatment of hypertensive patients with markedly elevated blood pressure (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg)."

Questions for the Sponsor

The Delegate raised a number of issues about which the sponsor should address in its pre-ADEC response. A number of these related to the product information and will not be discussed in this document. The issues are as follows:

- clarification of the issue of haemolysis in certain subjects' plasma samples
- clarification of the apparent discrepancy between the % of patients achieving BP control and the rates of individual SBP and DBP control in the pivotal study, CSPP100A-2204

Response from the Sponsor

In its pre-ADEC response, the sponsor addressed the issues described above.

In SPH100 biopharmaceutical studies, plasma samples which were described as "partially haemolysed" were reported only in studies CSPH100A2102 and CSPH100A2103. It is of note that the observation of a partially haemolysed sample is usually subjective, stating that a sample has a reddish-coloured appearance, as opposed to the normal amber-colour associated with plasma samples. Moreover the degree of haemolysis has not been elucidated.

Overall, the total number of partially haemolysed sample observations was less than 1% (13 out of 1960 samples for Study CSPH100A2102 and 17 out of 1848 samples for Study CSPH100A2103). There were only a few subjects in each study with more than one observed partially haemolysed sample. Of these samples, none met the standard Novartis criteria for repeat analysis (i.e. the observed value was 50% lower or two-fold higher than the expected concentration based on the surrounding sample concentration data). These criteria would have identified any significant change in the partially haemolysed samples which could have impacted bioanalytical, PK or statistical results.

In conclusion, based on the criteria set for the bioanalytical standard operation, the bioanalytical findings, and minimal number of haemolysed samples, it is believed that any potential impact of "partially haemolysed" plasma samples on these study results and conclusions would be negligible.

The following 3 sets of blood pressure control rates were assessed in Study CSPP100A2204:

• Overall BP control: patients had to have both systolic blood pressure (SBP) < 140 mmHg and diastolic blood pressure (DBP) < 90 mmHg to qualify as being controlled

• Individual SBP control: patients only needed to have SBP < 140 mmHg to qualify as being controlled

• Individual DBP control: patients only needed to have DBP < 90 mmHg to qualify as being controlled

Table 42 summarizes the rates of overall BP control, individual SBP control and individual DBP control. The rate of the BP control was slightly less when the criteria for overall BP control were used compared to when the criteria for the individual SBP or DBP control were used. This is expected because the overall BP control applied more stringent qualifying criteria than the individual SBP or DBP control, as described above. It is of note that the approximate difference between overall BP control rate and individual DBP or SBP control rates was generally consistent between treatment groups.

The percentage of patients achieving individual SBP control and individual DBP control were similar.

All doses of aliskiren/HCTZ combination produced greater BP control rates compared to the respective doses of the component monotherapies regardless of which BP control definition was used, clearly demonstrating the benefit of the combination.

In summary, the individual SBP and DBP control rates were consistent and the apparent discrepancy between the overall BP control rate and the individual BP control rates was due to the difference in the criteria defining the respective BP control rates. The aliskiren/amlodipine combination demonstrated greater BP control rate over the component monotherapies regardless of which BP control definition was used.

Table 42: Overall and individual BP Control rates (%) in patients whose BP was not controlled at the baseline – Study CSPP100A2204

	DBP control (msDBP<90 mmHg) rate	SBP control (msSBP<140 mmHg) rate	Overall BP control (msSBP/msDBP<140/90 mmHg) rate
Placebo	37.5%	34.1%	28.1%
Aliskiren 150mg	47.5%	49.4%	38.3%
Aliskiren 300mg	58.9%	58.0%	46.7%
HCTZ 12.5 mg	54.3%	47.1%	37.8%
HCTZ 25 mg	49.1%	48.7%	37.0%
Ali/HCTZ 150/12.5 mg	61.4%	59.7%	49.5%
Ali/HCTZ 150/25 mg	64.9%	69.3%	53.5%
Ali/HCTZ 300/12.5 mg	72.2%	65.8%	59.4%
Ali/HCTZ 300/25 mg	70.5%	69.3%	59.5%

Risk-Benefit Analysis

The most relevant EU guideline is CPMP/EWP-238/95 Rev. 2, *Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension*. For the claim of second line therapy, it is usually necessary to establish the following:

a statistically significant and clinically relevant additional blood pressure reduction on the fixed-dose combination in those patients who did not respond adequately to standard therapeutic doses of either monotherapy demonstration of statistically significant superior efficacy of the fixed-dose combination with no additional safety concerns outweighing the additional benefits of the fixed-dose combination from a parallel group comparison of the fixed-dose combination with the individual components at the same therapeutic doses.

For the purpose of the claim in second line therapy, all studies were well-designed and well-conducted. Parallel group comparison of the combination with the individual components using the same therapeutic doses in the pivotal study, CSPP100A-2204, demonstrated statistically significant superior efficacy of the combination. As well a number of studies demonstrated a statistically significant and clinically relevant additional blood pressure reduction of the combination in patients who did not respond adequately to standard therapeutic doses of either monotherapy.

The sponsor has provided some additional evidence of a supportive nature to substantiate a claim of maintenance of therapeutic effect of up to 12 months (Studies CSPP100A-2302 &-2302E1).

For the purpose of claiming efficacy as first line therapy, the above guideline is not so helpful. It addresses necessary (but not sufficient) conditions to be satisfied by any application in which first

line therapy is claimed. There are two conditions, firstly demonstration that each component has a documented contribution within the (fixed) combination using sub-therapeutic doses and secondly demonstration of a reduction of (dose-dependent) adverse drug reactions by the low-dose fixed combination as compared to the components in the lowest approved dosages.

The guideline does not address what would constitute the sufficient rather than necessary conditions for the proof of a first line claim. These would have to vary on a case-by-case basis and later in this section, the Delegate will raise particular points of concern regarding this application.

The first problem encountered when attempting to apply this guideline to this application is that not only is first line therapy being claimed but it is being claimed across the entire dosage range, from 150/12.5 mg to 300/25 mg. The sponsor would appear to argue that sufficient evidence has been adduced to demonstrate that each component has a documented contribution within the combination. However, it should be remembered that in the pivotal study for the primary diastolic endpoint, while most combination doses were statistically superior to their component monotherapies, there were some notable exceptions, all involving sub-therapeutic doses. The combination of aliskiren 150 mg/6.25 mg was not shown to be statistically significantly superior to either of its two monotherapy components and the combination aliskiren/hydrochlorothiazide 75 mg/12.5 mg was not shown to be statistically significantly superior to the monotherapy hydrochlorothiazide 12.5 mg. Furthermore, it is not so clear that a reduction of dose-dependent adverse drug reactions, when comparing the combination with the individual components, has been demonstrated. Rather what has been demonstrated is that there has been no increase when moving from components to combination. It should also be noted that pairwise comparison of the low-dose combination aliskiren/hydrochlorothiazide 150/12.5 mg and the monotherapy hydrochlorothiazide 12.5 mg for the parameter of % responders re msDBP did not show statistically significant superiority of the former over the latter.

However, the problems in applying particular guidelines are, in the view of the Delegate, only of minor concern, when one now looks at the actual evidence to support the claim.

Firstly, there is no data whatsoever in the dossier which actually compares directly the clinical efficacy and safety of the product given as a first line treatment with those same parameters when the product is given in response to an add-on indication. The latter strategy which by and large is accepted as clinical best practice is the one of careful dose titration. It is a strategy which allows the clinician to gauge the efficacy and safety at each step. Very importantly such a strategy allows one to isolate effects such as the degree of efficacy and particular adverse events and assign attribution. The sponsor in its response to the clinical evaluation report stated that it is important for this "hard-to-treat" population, i.e. those with stage (grade) 2 hypertension, to receive intensive therapy as early as possible to limit the period where the patient's blood pressure remains uncontrolled. This is simply speculation. At most the difference in time to onset of adequate effect between the so-called "intensive therapy" and the strategy of careful dose titration would be a matter of weeks. This has to be seen in the context of a condition which has been evolving over a much longer period of time, years in fact, particularly in a population from which has been excluded those with secondary forms of hypertension. There is no evidence in the dossier which demonstrates that there is any significant difference in clinical outcome between patients treated via either of the two strategies. There is in fact no clinical outcome data on morbidity or mortality.

Secondly, as noted by the evaluator, there was only one study, the pivotal study CSPP100A-2204, in which all patients randomized to the combination groups received the combination of aliskiren/hydrochlorothiazide as the initial treatment without titration from monotherapy. This immediately gives rise to a question about the design of the study. There was no guard against treatment at an unnecessarily high dose. Because of the lack of any dose-titration, there is an important flaw in the study design. If for example, a patient is randomized to the aliskiren/hydrochlorothiazide 150/25 mg group, there is still a reasonable chance that BP control

would have been achieved with aliskiren/hydrochlorothiazide 150/12.5 mg and even with aliskiren 150 mg monotherapy (see Table 11). In fact, given a 26.0% BP control rate (admittedly not statistically significant) with aliskiren 150 mg monotherapy, there is a 26/38 (68%) chance that a patient in the aliskiren/hydrochlorothiazide 150/12.5 mg group may have had his/her BP controlled with aliskiren 150 mg alone. Similarly, there is a 38/43 (88%) chance that a patient in the aliskiren/hydrochlorothiazide 150/25 mg group may have his/her BP controlled with the lower dose combination aliskiren/hydrochlorothiazide 150/12.5 mg. There was no difference between the BP control rates of aliskiren/hydrochlorothiazide 300/25 mg and 300/12.5 mg. In other words a patient was equally likely to have had his/her BP controlled by either of the latter two doses. All of these examples go against the generally established and well accepted clinical principle of treating with the lowest possible dose(s).

The Delegate noted the sponsor's argument that no additional analysis was performed in stage 2 patients that was not conducted as a pre-specified analysis in the overall population. Nonetheless the analyses done to support the initial therapy indication were *post hoc* in nature. As a general rule, one must always be very cautious with such analyses and particularly in relation to their use in support of an indication. The Delegate would be extremely reluctant to allow an indication which was supported by analyses which were not part of the pre-specified protocol.

The Delegate had great concerns about the wording of the original initial-treatment element of the indication, that is*:*

TRADENAME is indicated for the initial treatment of hypertensive patients unlikely to achieve control of blood pressure with a single agent".

How was a clinician expected to make a judgement of who was "*unlikely to achieve control of blood pressure with a single agent*"? Certainly, there is very little specific advice given in the PI and, as mentioned above, it does not guard against the possibility of treatment with unnecessarily high doses of the combination or even unnecessary treatment with the combination as opposed to a monotherapy.

The sponsor also clearly shared those concerns because it presented revised wording of the initial-treatment element of the indication in response to the TGA clinical evaluation report. The revised wording of the proposed first line indication is as follows:

TRADENAME is indicated for the initial treatment of hypertensive patients with markedly elevated blood pressure (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg)."

The Delegate had concerns about the wording, "*markedly elevated blood pressure*" as it is somewhat emotive and implies a degree of urgency which may not be justified. Blood pressures in the range of 160-180 over 100-110 are very common and may not warrant the term, "*markedly elevated*". However, this concern aside, the greatest problem by far with this indication is that the proof for it is based solely on patients with stage (grade) 2 hypertension, the latter being a relatively narrow window of hypertension possibilities. All patients with stage (grade) 3 hypertension and with secondary hypertension were excluded by protocol from participation in the pivotal study (and the other studies). There is no evidence whatsoever of the degree of efficacy of the combination aliskiren/hydrochlorothiazide therapies in the treatment of patients with grade 3 hypertension or with secondary hypertension or for that matter in the treatment of patients with grade 2 hypertension with for example, history of CVA, recent MI, current heart failure, angina requiring more than sublingual nitroglycerin, poorly controlled diabetes mellitus or renal impairment. The absence of any evidence in patients with grade 3 hypertension is inconsistent with such an indication.

For all of the above reasons, but particularly because of the absence of any patients with grade 3 hypertension in the pivotal study, the Delegate rejected the application for approval as first line therapy in patients with markedly elevated blood pressure.

Studies found that aliskiren/hydrochlorothiazide fixed-dose combination treatment to be safe and well tolerated in the short-term treatment of mild to moderate hypertension, up to a dose of 300/25 mg, with no unexpected adverse events or abnormalities. Satisfactory evidence of long-term safety was provided by Studies CSPP100A-2302 & -2302E1.

Overall, the Delegate was of the opinion that there is sufficient evidence of efficacy and safety to support the registration of the fixed-dose combination aliskiren/hydrochlorothiazide tablets, 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg, as second line therapy, that is, in patients whose blood pressure is not adequately controlled on monotherapy and as replacement therapy in patients already receiving aliskiren and hydrochlorothiazide from separate tablets at the same dose levels However, the Delegate is not convinced that there is sufficient evidence of efficacy to support the indication of initial treatment of hypertensive patients with markedly elevated blood pressure (systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg)..

The Delegate proposed to approve the submission for the indications of:

The treatment of hypertension. Treatment should not be initiated with these fixed dose combinations

TRADENAME is indicated as replacement therapy in patients already receiving aliskiren and hydrochlorothiazide from separate tablets at the same dose levels."

The Delegate proposed to reject that part of this submission for the indication of:

TRADENAME is indicated for the initial treatment of hypertensive patients with markedly elevated blood pressure (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg)."

The Delegate asked ADEC whether it agreed that the data provided are insufficient, particularly from an efficacy perspective, to allow approval of the fixed-dose combination product in the first line treatment of hypertension in people with markedly elevated blood pressure.

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal that the approved indication should be.

The treatment of hypertension. Treatment should not be initiated with these fixed dose combinations

In making this recommendation, ADEC agreed with the Delegate and the clinical evaluator that the data presented demonstrated statistically significant greater msDBP and msSBP reductions than their respective component monotherapies and placebo.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Rasilez HCT and Enviage HCT film-coated tablets containing aliskiren (as hemifumarate) / hydrochlorothiazide 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg, indicated for:

Treatment of hypertension. Treatment should not be initiated with these fixed dose combinations.

Attachment 1. Product Information

ENVIAGE HCT 150/12.5®
ENVIAGE HCT 150/25®
ENVIAGE HCT 300/12.5®
ENVIAGE HCT 300/25®

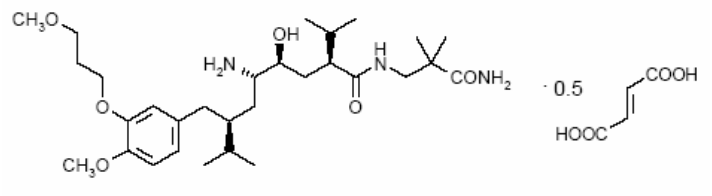
(aliskiren/hydrochlorothiazide)

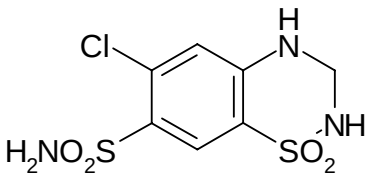
NAME OF THE MEDICINE

Active ingredients: Aliskiren, hydrochlorothiazide.

ENVIAGE HCT® is available in four strengths: ENVIAGE HCT 150/12.5®, ENVIAGE HCT 150/25®, ENVIAGE HCT 300/12.5® and ENVIAGE HCT 300/25®.

Structural formula:





Aliskiren (as hemifumarate)
CAS: 173334-58-2
Molecular formula: $C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$
Molecular weight: 609.8 (551.8 as free base)

Hydrochlorothiazide
CAS : 58-93-5
Molecular formula: $C_7H_8ClN_3O_4S_2$
Molecular weight: 297.72

DESCRIPTION

Aliskiren hemifumarate [2S,4S,5S,7S-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide] is a white to slightly yellowish powder. It is freely soluble in water, over a wide range of pH.

Hydrochlorothiazide [6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide] is structurally related to the thiazide group of diuretics. It is a white or almost white powder. Hydrochlorothiazide is very slightly soluble in water and freely soluble in dimethylsulfoxide.

ENVIAGE HCT 150/12.5 contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide; ENVIAGE HCT 150/25 contains 150 mg aliskiren (as hemifumarate)

and 25 mg hydrochlorothiazide; ENVIAGE HCT 300/12.5 contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide; ENVIAGE HCT 300/25 contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

Excipients:

ENVIAGE HCT 150/12.5: cellulose - microcrystalline, crospovidone, lactose, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol 4000, titanium dioxide.

ENVIAGE HCT 150/25: cellulose - microcrystalline, crospovidone, lactose, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol 4000, red iron oxide CI 77491, yellow iron oxide CI 77492, titanium dioxide.

ENVIAGE HCT 300/12.5: cellulose - microcrystalline, crospovidone, lactose, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol 4000, iron oxide black CI 77499, red iron oxide CI 77491, titanium dioxide.

ENVIAGE HCT 300/25: cellulose - microcrystalline, crospovidone, lactose, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol 4000, red iron oxide CI 77491, yellow iron oxide CI 77492, titanium dioxide.

PHARMACOLOGY

ENVIAGE HCT combines two antihypertensive compounds to control blood pressure in patients with essential hypertension: Aliskiren belongs to the class of direct rennin inhibitors and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these substances with complementary mechanism of action provide an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Pharmacodynamics

Aliskiren

Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

By inhibiting the enzyme renin, aliskiren inhibits the Renin-Angiotensin System (RAS) at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other agents that inhibit the

RAS (Angiotensin Converting Enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases plasma renin activities (PRA) in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive agents. Elevated PRA has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients. The clinical implications of the differences in effect on PRA are not known at the present time.

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment (12 months), and was independent of age, gender, body mass index and ethnicity.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the ACEI ramipril, the calcium channel blocker amlodipine, the angiotensin receptor antagonist valsartan, and the beta blocker atenolol. These combinations were efficacious and well tolerated.

Hydrochlorothiazide

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter perhaps by competing for the Cl- site, thereby affecting electrolyte reabsorption mechanisms:
- directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

Pharmacokinetics

Aliskiren

Following oral absorption, peak plasma concentrations of aliskiren are reached after 1 to 3 hours. The absolute bioavailability of aliskiren based on a pharmacokinetic study with capsule formulation is approximately 2.6%, however, this is indicative only as this figure refers to capsule/solution formulations and the precise value for the film coated tablets is unknown. Food reduces the C_{max} and exposure (AUC) but has minimal impact on pharmacodynamics thus can be taken without respect to food. High-fat meal significantly reduced the peak concentration (C_{max}) and total exposure (AUC) of aliskiren by 85% and 71% respectively, and the time to reach C_{max} was delayed by about 1 hour. Steady-state-plasma concentrations are reached within 5 to 7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose..

Aliskiren is evenly distributed systemically after oral administration. Following intravenous administration, mean volume of distribution at steady state is approximately 135 L indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47 to 51%) and independent of the concentration.

The mean elimination half-life is about 40 hours (range 34 to 41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (91%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, the mean plasma clearance is approximately 9 L/h.

Exposure to aliskiren increased more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and Cmax, respectively. At steady state the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Hydrochlorothiazide

The absorption of hydrochlorothiazide after an oral dose is rapid (T_{max} about 2 hours), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60-80% after oral administration.

The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated administration, and accumulation is minimal when administered once daily.

The distribution and elimination kinetics have generally been described by a biexponential decay function, with a terminal half-life of 6-15 hours. Greater than 95% of the absorbed dose is excreted as unchanged compound in the urine.

Aliskiren/Hydrochlorothiazide

Following oral administration of ENVIAGE HCT combination tablets, the median peak plasma concentration time are within 1 hour for aliskiren and 2.5 hours for hydrochlorothiazide.

The rate and extent of absorption of ENVIAGE HCT are equivalent to the bioavailability of aliskiren and hydrochlorothiazide when administered as individual monotherapies. Similar food effect was observed for ENVIAGE HCT as for the individual monotherapies. When taken with a high fat meal, mean AUC and C_{max} of aliskiren are decreased by 60% and 82%, respectively. As a result, patients should establish a routine pattern for taking ENVIAGE HCT with regard to meals and should be advised that food can markedly decrease absorption of aliskiren.

Pharmacokinetics in special patient groups: Pharmacokinetics in special patient groups: ENVIAGE HCT is an effective once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity**.**

Pharmacokinetics in the elderly: No adjustment of the initial dose of ENVIAGE HCT is required for elderly patients (see 'DOSAGE AND ADMINISTRATION').

Pharmacokinetics in children: No pharmacokinetic data are available in the paediatric population.

Pharmacokinetics in patients with impaired hepatic function: The pharmacokinetics of aliskiren and hydrochlorothiazide are not significantly affected in patients with mild to moderate liver disease. Consequently, no initial dose adjustment of ENVIAGE HCT is required in patients with mild to moderate hepatic impairment. No data are available on patients with severe hepatic impairment when treated by ENVIAGE HCT. However, because of hydrochlorothiazide, ENVIAGE HCT is contraindicated in patients with severe hepatic impairment (see 'CONTRAINDICATIONS').

Pharmacokinetics in patients with impaired renal function: No dose adjustment is required for patients with mild to moderate renal impairment (see section 4.4 Special warnings and precautions for use and 4.2 Posology and Method of administration). No data are available for ENVIAGE HCT in patients with severe renal impairment (creatinine clearance < 30 mL/min). However, as expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide. Therefore, ENVIAGE HCT is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see 'CONTRAINDICATIONS').

CLINICAL TRIALS

Over 3,900 hypertensive patients received ENVIAGE HCT once daily in clinical trials.

In hypertensive patients, once-daily administration of ENVIAGE HCT provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks. The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. The antihypertensive effect of a single dose of the combination persisted for 24 hours. Upon withdrawal of the aliskiren treatment (aliskiren with or without hydrochlorothiazide add-on), the return of blood pressure towards baseline was gradual (3-4 weeks) with no evidence of the rebound effect.

ENVIAGE HCT was studied in a placebo-controlled trials including 2,762 hypertensive patients with diastolic blood pressure ≥ 95 mmHg and < 110 mmHg (mean baseline blood pressure of 153.6/99.2 mmHg). In this study, ENVIAGE HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg produced dose-dependent blood pressure reductions (systolic/diastolic) from 17.6/11.9 mmHg to 21.2/14.3 mmHg, respectively, compared to 7.5/6.9 mmHg with placebo. The greater blood pressure reductions with these combination doses were also significantly greater than the respective doses of aliskiren and hydrochlorothiazide when used alone. The combination of aliskiren and hydrochlorothiazide neutralised the reactive increase of PRA caused by hydrochlorothiazide.

When administered to patients with grade 2 hypertension (systolic BP 160-179 mmHg and diastolic BP 100-109 mm Hg), , ENVIAGE HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg demonstrated significantly greater systolic/diastolic blood pressure control rates (< 140/90 mmHg) as compared to the respective monotherapies. In this population, ENVIAGE HCT 150 mg/12.5 mg to 300 mg/25 mg provided dose-dependent systolic/diastolic blood pressure reduction from 20.6/12.4 mmHg to 24.8/14.5 mmHg, which were significantly superior to the respective monotherapies. The safety of the combination therapy was similar to the respective monotherapies regardless of severity of hypertension. Hypotension and related adverse events were uncommon with the combination treatment and, with no increased incidence in elderly patients.

In a study in 880 randomised patients not adequately responsive to aliskiren 300 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 15.8/11.0 mmHg, which were significantly greater than aliskiren 300 mg monotherapy. In a study in 722 randomised patients not adequately responsive to hydrochlorothiazide 25 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 16.78/10.7 mmHg, which were significantly greater than hydrochlorothiazide 25 mg monotherapy.

In another clinical trial, the efficacy and safety of ENVIAGE HCT were also assessed in 489 obese hypertensive patients who did not respond to hydrochlorothiazide 25 mg (baseline systolic/diastolic blood pressure 149.4/96.8 mmHg). In this difficult-to-treat population, ENVIAGE HCT provided a blood pressure reduction (systolic/diastolic) of 15.8/11.9 mmHg compared to 15.4/11.3 mmHg for irbesartan/hydrochlorothiazide, 13.6/10.3 mmHg for amlodipine/hydrochlorothiazide and 8.6/7.9 mmHg for hydrochlorothiazide monotherapy, with similar safety to hydrochlorothiazide monotherapy.

INDICATIONS

Treatment of hypertension.
Treatment should not be initiated with these fixed dose combinations.

CONTRAINDICATIONS

- Hypersensitivity to any of the components of ENVIAGE HCT and to other sulfonamide derived drugs;
- Pregnancy (see 'Use in Pregnancy');
- Severe hepatic impairment;
- Severe renal impairment (creatinine clearance <30 mL/min);
- Anuria;
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.
- History of Angioedema with aliskiren;
- Concomitant administration with cyclosporine, a highly potent P-gp inhibitor, and other potent P-gp inhibitors such as verapamil and quinidine (see 'PRECAUTIONS - Interactions with Other Drugs').

PRECAUTIONS

Serum electrolyte changes: Based on experience with the use of other substances that affect the renin-angiotensin system (RAS), concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) should be used with caution. Hypokalaemia has been reported during treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended. The renin-aldosterone link is mediated by angiotensin II, so with coadministration of aliskiren the reduction in serum potassium is less pronounced than observed under monotherapy with hydrochlorothiazide (see 'PRECAUTIONS – Interactions', and 'ADVERSE REACTIONS').

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals. Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hypokalaemia, hyponatraemia and hypochloraemic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Warning signs of fluid or electrolyte imbalance are dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with aliskiren may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH).

Conversely, due to the aliskiren component of ENVIAGE HCT, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with ENVIAGE HCT, risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Caution is required when co-administering potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes with ENVIAGE HCT.

There is no evidence that ENVIAGE HCT would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Sodium and/or volume depleted patients: In patients with marked volume- and/or salt-depletion (e.g. those receiving high doses of diuretics) symptomatic hypotension could occur after initiation of treatment with ENVIAGE HCT. This condition should be corrected prior to administration of ENVIAGE HCT, or the treatment should start under close medical supervision.

Angioedema: As with other agents acting on the renin-angiotensin system, angioedema has been reported rarely in patients treated with aliskiren. If angioedema occurs, ENVIAGE HCT should be promptly discontinued and appropriate therapy and monitoring provided until

complete and sustained resolution of signs and symptoms has occurred. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to ensure patient airways should be provided.

Impaired renal function: When ENVIAGE HCT is used in patients with impaired renal function, periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. There is no experience regarding the administration of ENVIAGE HCT in patients who have recently undergone kidney transplantation. No dosage adjustment is necessary in patients with renal impairment whose GFR is ≥ 30 ml/min/1.73 m2. However, in patients with mild to moderate renal impairment (GFR ≥ 30 ml/min/1.73 m2 but < 60 ml/min/1.73 m2), ENVIAGE HCT should be administered with caution.

As for other agents acting on the renin-angiotensin system, caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (eg. Due to blood loss, severe prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease or kidney disease. Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Renal artery stenosis: No data are available on the use of ENVIAGE HCT in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. However, as with other agents acting on the renin-angiotensin system, there is an increased risk of renal insufficiency, including renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

Hepatic impairment: Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with Enviage HCT in patients with hepatic impairment.

Systemic lupus erythematosus: Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances: Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may occur during thiazide therapy. To date,

no data are available from clinical studies that were specifically-designed to evaluate the safety of ENVIAGE HCT in diabetic patients .
Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Heart failure: Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV). ENVIAGE HCT should be used with caution in patients with heart failure due to limited clinical efficacy and safety data.

General: In the event of severe and persistent diarrhoea, ENVIAGE HCT therapy should be stopped.
As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.
Hypersensitivity reactions to hydrochlorothiazide may occur, but are more likely in patients with a prior history allergy or bronchial asthma.such a history.

Excipients : ENVIAGE HCT contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. ENVIAGE HCT contains wheat starch. It is suitable for people with coeliac disease. Patients with wheat allergy (different from coeliac disease) should not take this medicine.

Effects on ability to drive and use machines: As with other antihypertensive agents, it is advisable to exercise caution when driving or operating machinery.

Genotoxicity: The combination of aliskiren and hydrochlorothiazide has not been tested for mutagenicity or clastogenicity.

Aliskiren

Aliskiren was negative in a series of assays for gene mutation, chromosomal damage and DNA damage.

Hydrochlorothiazide

Hydrochlorothiazide did not iduce gene mutation in bacteria or chromosome damage in mammalian cells in several in vitro and in vivo assays. However, positive results were obtained in a mammalian cell assay for gene mutation (mouse lymphoma cell assay) and in two other tests (sister chromatid exchange assay in Chinese hamster ovary cells and nondisjunction assay in Aspergillus nidu/ans).

Carcinogenicity: The combination of aliskiren and hydrochlorothiazide has not been tested for carcinogenicity.

Aliskiren

The carcinogenic potential of aliskiren was assessed in a 2-year rat study and a 6-month transgenic mouse study. There was no significant increase in the incidence of neoplastic lesions in mice given up to 1500 mg/kg/day PO (ER <1 based on AVC). Inflammatory and proliferative changes were observed in the lower gastro-intestinal tract at dietary doses of 750 or 1500 mg/kg/day in both mice and rats (ER <I and 3 based on AVC, respectively). One colonic adenoma and one caecal adenocarcinoma were found in two separate rats at the dietary dose of 1500 mg/kg/day (ER 3 based on AVe). These tumour incidences were not statistically significant although these tumours were considered relatively rare when compared to the historical controls. The low absorption and biliary excretion of aliskiren in rats resulted in high local concentrations in the gastrointestinal tract. The faecal concentration in rats treated with a dose of 1500 mg/kg/day for a month was about 57 fold higher than the human faecal concentration (mg/g) at the MRHD. Overall, the data suggests that these tumour incidences may not be clinical relevant.

Hydrochlorothiazide

Two-year feeding studies in mice and rats showed no evidence of carcinogenic potential for hydrochlorothiazide in female mice at doses up to approximately 600 mg/kg/day, or in male and female rats at doses up to approximately 100 mg/kg/day. However, there was equivocal evidence for hepatocarcinogenicity in male mice treated with hydrochlorothiazide at approximately 600 mg/kg/day.

Use in Pregnancy (Category D)

There is no clinical experience with the use of ENVIAGE HCT in pregnant women.

Aliskiren

Aliskiren should not be used during pregnancy or in women planning to become pregnant. Physicians prescribing any agents acting on the RAAS (reninangiotensinaldosterone system) should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, ENVIAGE HCT should be discontinued as soon as possible.

Drugs that act on the RAAS can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors (a specific

class of drugs acting on the RAAS). When pregnancy is detected, ENVIAGE HCT should be discontinued as soon as possible.

The use of drugs that act directly on the RAAS during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydraminos has been reported, presumably resulting from decreased fetal renal function. Oligohydraminos in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus
arteriosis have also been reported, although it is not clear whether these occurrences were due to exposure to the drug, In addition. in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects.

Infants with histories of in utero exposure to renin inhibitor should be closely observed for hypotension. oliguria and hyperkalemia.

Aliskiren was not teratogenic when administered at matemotoxic oral doses of 543 mg/kg/day to rats or 90 mg/kg/day to rabbits. An embryofetal NOAEL was established in rats with an oral dose of 270 mg/kg/day and in rabbits with 90 mg/kg/day, equivalent to <1. and 4- fold the MRHD based on AUC, respectively. Post-natal development in rats was unaffected by oral doses up to 181 mg/kg/day (ER <1. based on AUC).

Hydrochlorothiazide

Intrauterine exposure to thiazide diuretics is associated with fetal or neonatal thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults.

Use in Lactation

ENVIAGE HCT is not recommended during lactation. It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. Hydrochlorothiazide is excreted into breast milk. Because of the potential for adverse effects on the breast-fed infant, a decision should be made whether to discontinue breast-feeding or discontinue use of ENVIAGE HCT, taking in account the importance of both the control of hypertension and breast-feeding to the mother and infant

Interactions with Other Drugs

ENVIAGE HCT

Co-administration of aliskiren and hydrochlorothiazide does not cause meaningful changes in the steady-state pharmacokinetic exposure (AUC) and the maximum concentration (Cmax) of both components in healthy volunteers.

Medicinal products affecting potassium: The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of aliskiren. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium, corticosteroids, ACTH, salicylic acid derivatives). Conversely, based on experience with the use of other medicinal products that blunt the renin-angiotensin system (RAS), concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. Adequate monitoring of serum potassium in patients at risk is recommended.

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium is recommended when ENVIAGE HCT is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

Aliskiren

Aliskiren has a low potential for clinically relevant interactions with medicinal products commonly used to treat hypertension or diabetes.

Compounds that have been investigated in clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, fenofibrate, pioglitazone, allopurinol, isosorbide- 5-mononitrate, ramipril and hydrochlorothiazide and no clinically significant interactions have been observed.

Co-administration of aliskiren with either valsartan (decrease of 28%), metformin (decrease of 28%), amlodipine (increase of 29%) or cimetidine (increase of 19%) resulted in between 20% and 30% change in C_{max} or AUC of aliskiren. Co-administration of aliskiren had no significant impact on atorvastatin, valsartan, metformin or amlodipine pharmacokinetics. As a result no dose adjustment for aliskiren or these co-administered medications is necessary.

Co-administration of irbesartan reduced aliskiren Cmax up to 50% after multiple dosing. Preliminary data suggest that irbesartan may decrease aliskiren AUC and Cmax. Digoxin bioavailability may be slightly decreased by aliskiren.

In experimental animals it has been shown that Pgp is a major determinant of aliskiren bioavailability. Inducers of Pgp (St John's wort, rifampicin) might therefore decrease the bioavailability of aliskiren.

CYP 450 interactions: At expected therapeutic concentrations aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and CYP3A). Aliskiren does not induce CYP3A4. Aliskiren is metabolised minimally by the cytochrome P450 enzymes CYP3A4, CYP3A5, and CYP2D6, therefore aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce, or are metabolised by these enzymes.

P glycoprotein interactions: *In vitro* studies indicate that MDR1 (Pgp) was found to be the major efflux transporter system involved in absorption and disposition of aliskiren.. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter.

Pgp substrates or weak inhibitors: No relevant interactions with atenolol, digoxin, amlodipine, and cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by 50%.

Pgp moderate inhibitors: Co-administration of ketoconazole (200 mg) with aliskiren (300 mg) resulted in a 80% increase in plasma levels of aliskiren (AUC and C_{max}). Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Co-administration of a single oral dose of 300 mg aliskiren with 240 mg verapamil increased AUC and Cmax of aliskiren by ~2-fold. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. As a result no dose adjustment for aliskiren is necessary.

Potent Pgp potent inhibitors: A single dose drug interaction study in healthy subjects has shown that cyclosporin A (200 and 600 mg) increases Cmax of aliskiren 75 mg by approximately 2.5 fold and the AUC by approximately 5-fold. Therefore, the concomitant use of both drugs is contraindicated.

Furosemide: When aliskiren was co-administered with frusemide, the AUC and Cmax of furosemide were reduced by 28% and 49% respectively. It is therefore recommended that the effects be monitored when initiating and adjusting frusemide therapy to avoid possible under-utilisation in clinical situations of volume overload.

Non-steroidal anti-inflammatory drugs (NSAIDs): As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients)

aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination of aliskiren with an NSAID requires caution, especially in elderly patients.

Potassium and potassium sparing diuretics: Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of aliskiren with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other substances that may increase serum potassium levels (e.g. heparin) may lead to increases in serum potassium. If co-medication is considered necessary, caution is advisable (see 'ADVERSE REACTIONS').

Warfarin: The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

Food intake: Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially.

Hydrochlorothiazide

Lithium: Should not generally be given with diuretics. Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazides. There is no experience with concomitant use of aliskiren and lithium. Therefore, monitoring of serum lithium concentrations is recommended during concurrent use.

Curare derivatives: Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.

Non-steroidal anti-inflammatory drugs: Concomitant administration of NSAIDs (e.g. salicylic acid derivative, indomethacin) may weaken the diuretic and antihypertensive activity of the thiazide component of ENVIAGE HCT. Concurrent hypovolaemia may induce acute renal failure.

Medicinal products affecting potassium: The hypokalaemic effect of diuretics may be increased by kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives.

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesemia may occur as unwanted effects, favouring the onset of digitalis-induced cardiac arrhythmias.

Antidiabetic medicinal products: It may prove necessary to readjust the dosage of insulin and of oral antidiabetic agents.

Anticholinergic agents: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.

Methyldopa: There have been reports in the literature of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Cholestyramine: Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine.

Vitamin D and calcium salts: Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

Cyclosporin: Concomitant treatment with cyclosporin may increase the risk of hyperuricaemia and gout-type complications.

Carbamazepine: Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatraemia. Such patients should therefore be advised about the possibility of hyponatraemic reactions, and should be monitored accordingly.

Other interactions: Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol, may increase the risk of adverse effects caused by amantadine, may enhance the hyperglycaemic effect of diazoxide, and may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

ADVERSE EFFECTS

The safety of ENVIAGE HCT has been evaluated in 9 clinical trials with more than 3900 patients, including over 700 treated for over 6 months, and 190 for over 1 year. The incidence of adverse events showed no association with gender, age, body mass index, race or ethnicity. Treatment with ENVIAGE HCT had an overall incidence of adverse experiences at doses up to 300 mg/25 mg similar to placebo. Adverse events have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most frequent adverse drug reaction with aliskiren/hydrochlorothiazide is diarrhoea.

Table 1 Number (%) of patients with most frequent Adverse Events (> 2% for any group) by preferred term (in short term, double-blind all controlled studies) (safety population).

Preferred term	Placebo N=193 n (%)	Aliskiren N=973 n (%)	HCTZ N=1075 n (%)	Aliskiren/HCTZ 150/12.5 mg N=184 n (%)	Aliskiren/HCTZ 150/25 mg N=719 n (%)	Aliskiren/HCTZ 300/12.5 mg N=474 n (%)	Aliskiren/HCTZ 300/25 mg N=1030 n (%)
Any adverse experience	**85 (44.0)**	**312 (32.1)**	**420 (39.1)**	**72 (39.1)**	**228 (31.7)**	**135 (28.5)**	**297 (28.8)**
Headache	26 (13.5)	56 (5.8)	61 (5.7)	15 (8.2)	21 (2.9)	22 (4.6)	28 (2.7)
Nasopharyngitis	10 (5.2)	25 (2.6)	42 (3.9)	3 (1.6)	22 (3.1)	9 (1.9)	28 (2.7)
Dizzines	2 (1.0)	6 (0.6)	21 (2.0)	6 (3.3)	10 (1.4)	12 (2.5)	17 (1.7)
Influenza	3 (1.6)	12 (1.2)	9 (0.8)	1 (0.5)	10 (1.4)	4 (0.8)	12 (1.2)
Diarrhoea	1 (0.5)	14 (1.4)	20 (1.9)	1 (0.5)	10 (1.4)	10 (2.1)	8 (0.8)
Back pain	5 (2.6)	10 (1.0)	14 (1.3)	2 (1.1)	6 (0.8)	5 (1.1)	10 (1.0)
Arthralgia	1 (0.5)	7 (0.7)	11 (1.0)	1 (0.5)	6 (0.8)	4 (0.8)	7 (0.7)
Bronchitis	3 (1.6)	11 (1.1)	10 (0.9)	4 (2.2)	4 (0.6)	4 (0.8)	7 (0.7)
Cough	1 (0.5)	5 (0.5)	10 (0.9)	2 (1.1)	7 (1.0)	2 (0.4)	6 (0.6)
Vertigo	1 (0.5)	6 (0.6)	7 (0.7)	1 (0.5)	4 (0.6)	5 (1.1)	12 (1.2)
Nausea	4 (2.1)	4 (0.4)	10 (0.9)	2 (1.1)	5 (0.7)	3 (0.6)	4 (0.4)
Asthenia	0 (0.0)	8 (0.8)	7 (0.7)	1 (0.5)	3 (0.4)	3 (0.6)	4 (0.4)
Fatigue	2 (1.0)	6 (0.6)	13 (1.2)	1 (0.5)	4 (0.6)	2 (0.4)	6 (0.6)
Oedema peripheral	1 (0.5)	11 (1.1)	13 (1.2)	2 (1.1)	2 (0.3)	3 (0.6)	5 (0.5)
Sinusitis	1 (0.5)	3 (0.3)	1 (0.1)	1 (0.5)	4 (0.6)	3 (0.6)	2 (0.2)
Vomiting	4 (2.1)	1 (0.1)	5 (0.5)	3 (1.6)	4 (0.6)	0 (0.0)	1 (0.1)
Flatulence	1 (0.5)	4 (0.4)	4 (0.4)	0 (0.0)	1 (0.1)	1 (0.2)	2 (0.2)
Angina pectoris	0 (0.0)	1 (0.1)	2 (0.2)	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)
Myocardial infarction	0 (0.0)	0 (0.00	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Tendonitis	0 (0.0)	4 (0.4)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)

N=number of patients, n=number with AEs, %=(n/N)*100.

Additional information on the combination

Diarrhoea: Diarrhoea is a dose-related adverse drug reaction for aliskiren. Doses above aliskiren 300 mg did not give an increased blood pressure response but increased the rate of diarrhoea. In controlled clinical trials, the incidence of diarrhoea in ENVIAGE HCT treated patients was low and not more than that in aliskiren or hydrochlorothiazide treated patients.

Serum potassium: In a large placebo-controlled clinical trial, the opposing effects of aliskiren (150 mg or 300 mg) and hydrochlorothiazide (12.5 mg or 25 mg) on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant.

Periodic determinations of serum potassium to detect possible electrolyte imbalance should be performed at appropriate intervals.

Additional information on individual components

Adverse reactions previously reported with one of the individual components may occur with ENVIAGE HCT even if not observed in clinical trials.

Aliskiren

Treatment with aliskiren was well tolerated with an overall incidence of adverse experiences similar to placebo up to 300 mg. Adverse events have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common adverse drug reaction is diarrhoea. Other adverse drug reactions that occurred during treatment with aliskiren include rash and angioedema. In controlled clinical trials, angioedema occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or hydrochlorothiazide. In the event of any signs suggesting an allergic reaction (in particular difficulties in breathing, or swallowing, or swelling of the face, extremities, eyes, lips and/or tongue) patients should discontinue treatment and contact the physician. The incidence of cough was similar in placebo (0.6%) and aliskiren treated (0.9%) patients.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/L and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other agents acting on the renin-angiotensin system, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers. These decreases led to slight increases in rates of anaemia with aliskiren compared to placebo (0.1% for any aliskiren use vs 0% for placebo).

Serum potassium: Increases in serum potassium were minor and infrequent in patients with essential hypertension treated with aliskiren alone (0.9% compared to 0.6% with placebo). However, in one study where aliskiren was used in combination with an angiotensin converting enzyme inhibitor (ACEI) in a diabetic population increases in serum potassium were more frequent (5.5%). Therefore as with any agent acting on the RAS system, routine monitoring of electrolytes and renal function is indicated in the diabetic population and those with kidney disease and heart failure when using aliskiren.

Hydrochlorothiazide

Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in ENVIAGE HCT. The following adverse experiences have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide irrespective of their causal association with the study drug:

Electrolyte and metabolic disorders (see 'PRECAUTIONS').

Common: Urticaria and other forms of rash, loss of appetite, mild nausea and vomiting, postural hypotension, which may be aggravated by alcohol, anaesthetics or sedatives, and impotence.

Rare: Photosensitisation, abdominal distress, constipation, diarrhoea, and gastrointestinal discomfort, intrahepatic cholestasis or jaundice, cardiac arrhythmias, headache, dizziness or lightheadedness, sleep disturbances, depression, paraesthesia, disturbances of vision, and thrombocytopenia, sometimes with purpura.

Very rare: Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, pancreatitis, leukopenia, agranulocytosis, bone marrow depression, haemolytic anaemia, hypersensitivity reactions, respiratory distress including pneumonitis and pulmonary oedema.

DOSAGE AND ADMINISTRATION

The dose of ENVIAGE HCT must be determined by careful titration of the dose of each of the individual components. The recommended dose is one tablet per day, one of Enviage HCT 150/12.5 or Enviage HCT 150/25 or Enviage HCT 300/12.5 or Enviage HCT 300/25 mg. The maximum recommended dose of the combination therapy is 300/25 mg once daily.

The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.

Patients should establish a routine pattern for taking ENVIAGE HCT with regard to meals. ENVIAGE HCT should be taken with light meals. Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially.

Patients not adequately treated on monotherapy

A patient whose blood pressure is not adequately controlled on monotherapy may be switched to the combination therapy with ENVIAGE HCT. When clinically appropriate direct change from monotherapy to ENVIAGE HCT fixed combination may be considered.

Patients adequately treated with separate tablets of Aliskiren and Hydrochlorothiazide

For convenience, patients already receiving aliskiren and hydrochlorothiazide from separate tablets may be switched to a single tablet of ENVIAGE HCT containing the same component doses.

Renal impairment: No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see 'PRECAUTIONS - Impaired renal function' and 'PHARMACOLOGY – Pharmacokinetics'). Due to the hydrochlorothiazide component, ENVIAGE HCT is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see 'CONTRAINDICATIONS' and 'PHARMACOLOGY – Pharmacokinetics').

Hepatic impairment: No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment (see 'PHARMACOLOGY – Pharmacokinetics'). Due to the hydrochlorothiazide component, ENVIAGE HCT is contraindicated in patients with severe hepatic impairment (see 'CONTRAINDICATIONS').

Use in elderly patients (over 65 years): No initial dosage adjustment is required for elderly patients.

Use in children and adolescents: The safety and efficacy of ENVIAGE HCT has not been established in children and adolescents (below 18 years of age) and therefore ENVIAGE HCT is not recommended in this population.

OVERDOSAGE

No data are available related to overdose in humans. The most likely manifestations of overdosage would be hypotension, related to the antihypertensive effect of aliskiren and hydrochlorothiazide. If symptomatic hypotension should occur, supportive treatment should be initiated.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

ENVIAGE HCT 150/12.5: White, biconvex, ovaloid film-coated tablet imprinted with LCI on one side and NVR on the other side. Packs of 7, 14, 28, 30, 49, 50, 56, 90, 98, and 280.

ENVIAGE HCT 150/25: Pale yellow, biconvex, ovaloid film-coated tablet imprinted with CLL on one side and NVR on the other side. Packs of 7, 14, 28, 30, 49, 50, 56, 90, 98, and 280.

ENVIAGE HCT 300/12.5: Violet white, biconvex ovaloid film-coated tablet imprinted with CVI on one side and NVR on the other side. Packs of 7, 14, 28, 30, 49, 50, 56, 90, 98, and 280.

ENVIAGE HCT 300/25: Light yellow, biconvex, ovaloid film- coated tablet imprinted with CVV on one side and NVR on the other side. Packs of 7, 14, 28, 30, 49, 50, 56, 90, 98, and 280.

Not all pack sizes may be marketed.

Storage: Keep in the original package. Store below 30°C. Protect from moisture. Protect from light.

Poisons schedule: S4

SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
North Ryde NSW 2113

® = Registered Trademark

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration: 4 February 2010

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enh280110i.doc based on the CDS of 22 November 2007, the Non-clinical (15/04/09) and clinical (01/05/09) recommendations and Novartis response to the CER dated 30 May 2009 an d to S31 No. 2008-2072-3-pce-5 dated 02 September 2009 and the Delegate's Overview dated 23 October 2009 and email dated 27/01/10.

RASILEZ HCT 150/12.5®
RASILEZ HCT 150/25®
RASILEZ HCT 300/12.5®
RASILEZ HCT 300/25®

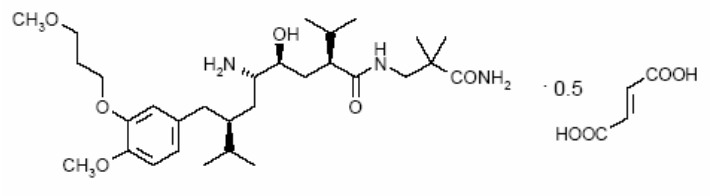
(aliskiren/hydrochlorothiazide)

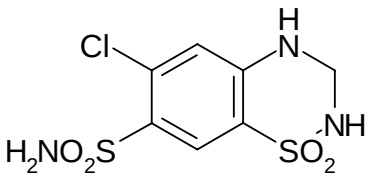
NAME OF THE MEDICINE

Active ingredients: Aliskiren, hydrochlorothiazide.

RASILEZ HCT® is available in four strengths: RASILEZ HCT 150/12.5®, RASILEZ HCT 150/25®, RASILEZ HCT 300/12.5® and RASILEZ HCT 300/25®.

Structural formula:





Aliskiren (as hemifumarate)
CAS: 173334-58-2
Molecular formula: $C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$
Molecular weight: 609.8 (551.8 as free base)

Hydrochlorothiazide
CAS : 58-93-5
Molecular formula: $C_7H_8ClN_3O_4S_2$
Molecular weight: 297.72

DESCRIPTION

Aliskiren hemifumarate [2S,4S,5S,7S-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide] is a white to slightly yellowish powder. It is freely soluble in water, over a wide range of pH.

Hydrochlorothiazide [6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide] is structurally related to the thiazide group of diuretics. It is a white or almost white powder. Hydrochlorothiazide is very slightly soluble in water and freely soluble in dimethylsulfoxide.

RASILEZ HCT 150/12.5 contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide; RASILEZ HCT 150/25 contains 150 mg aliskiren (as hemifumarate)

and 25 mg hydrochlorothiazide; RASILEZ HCT 300/12.5 contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide; RASILEZ HCT 300/25 contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

Excipients:

RASILEZ HCT 150/12.5: cellulose - microcrystalline, crospovidone, lactose, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol 4000, titanium dioxide.

RASILEZ HCT 150/25: cellulose - microcrystalline, crospovidone, lactose, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol 4000, red iron oxide CI 77491, yellow iron oxide CI 77492, titanium dioxide.

RASILEZ HCT 300/12.5: cellulose - microcrystalline, crospovidone, lactose, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol 4000, iron oxide black CI 77499, red iron oxide CI 77491, titanium dioxide.

RASILEZ HCT 300/25: cellulose - microcrystalline, crospovidone, lactose, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol 4000, red iron oxide CI 77491, yellow iron oxide CI 77492, titanium dioxide.

PHARMACOLOGY

RASILEZ HCT combines two antihypertensive compounds to control blood pressure in patients with essential hypertension: Aliskiren belongs to the class of direct rennin inhibitors and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these substances with complementary mechanism of action provide an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Pharmacodynamics

Aliskiren

Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

By inhibiting the enzyme renin, aliskiren inhibits the Renin-Angiotensin System (RAS) at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other agents that inhibit the

RAS (Angiotensin Converting Enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases plasma renin activities (PRA) in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive agents. Elevated PRA has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients. The clinical implications of the differences in effect on PRA are not known at the present time.

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment (12 months), and was independent of age, gender, body mass index and ethnicity.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the ACEI ramipril, the calcium channel blocker amlodipine, the angiotensin receptor antagonist valsartan, and the beta blocker atenolol. These combinations were efficacious and well tolerated.

Hydrochlorothiazide

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter perhaps by competing for the Cl- site, thereby affecting electrolyte reabsorption mechanisms:
- directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

Pharmacokinetics

Aliskiren

Following oral absorption, peak plasma concentrations of aliskiren are reached after 1 to 3 hours. The absolute bioavailability of aliskiren based on a pharmacokinetic study with capsule formulation is approximately 2.6%, however, this is indicative only as this figure refers to capsule/solution formulations and the precise value for the film coated tablets is unknown. Food reduces the C_{max} and exposure (AUC) but has minimal impact on pharmacodynamics thus can be taken without respect to food. High-fat meal significantly reduced the peak concentration (C_{max}) and total exposure (AUC) of aliskiren by 85% and 71% respectively, and the time to reach C_{max} was delayed by about 1 hour. Steady-state-plasma concentrations are reached within 5 to 7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose..

Aliskiren is evenly distributed systemically after oral administration. Following intravenous administration, mean volume of distribution at steady state is approximately 135 L indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47 to 51%) and independent of the concentration.

The mean elimination half-life is about 40 hours (range 34 to 41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (91%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, the mean plasma clearance is approximately 9 L/h.

Exposure to aliskiren increased more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and Cmax, respectively. At steady state the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Hydrochlorothiazide

The absorption of hydrochlorothiazide after an oral dose is rapid (T_{max} about 2 hours), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60-80% after oral administration.

The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated administration, and accumulation is minimal when administered once daily.

The distribution and elimination kinetics have generally been described by a biexponential decay function, with a terminal half-life of 6-15 hours. Greater than 95% of the absorbed dose is excreted as unchanged compound in the urine.

Aliskiren/Hydrochlorothiazide

Following oral administration of RASILEZ HCT combination tablets, the median peak plasma concentration time are within 1 hour for aliskiren and 2.5 hours for hydrochlorothiazide.

The rate and extent of absorption of RASILEZ HCT are equivalent to the bioavailability of aliskiren and hydrochlorothiazide when administered as individual monotherapies. Similar food effect was observed for RASILEZ HCT as for the individual monotherapies. When taken with a high fat meal, mean AUC and C_{max} of aliskiren are decreased by 60% and 82%, respectively. As a result, patients should establish a routine pattern for taking RASILEZ HCT with regard to meals and should be advised that food can markedly decrease absorption of aliskiren.

Pharmacokinetics in special patient groups: Pharmacokinetics in special patient groups: RASILEZ HCT is an effective once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity**.**

Pharmacokinetics in the elderly: No adjustment of the initial dose of RASILEZ HCT is required for elderly patients (see 'DOSAGE AND ADMINISTRATION').

Pharmacokinetics in children: No pharmacokinetic data are available in the paediatric population.

Pharmacokinetics in patients with impaired hepatic function: The pharmacokinetics of aliskiren and hydrochlorothiazide are not significantly affected in patients with mild to moderate liver disease. Consequently, no initial dose adjustment of RASILEZ HCT is required in patients with mild to moderate hepatic impairment. No data are available on patients with severe hepatic impairment when treated by RASILEZ HCT. However, because of hydrochlorothiazide, RASILEZ HCT is contraindicated in patients with severe hepatic impairment (see 'CONTRAINDICATIONS').

Pharmacokinetics in patients with impaired renal function: No dose adjustment is required for patients with mild to moderate renal impairment (see section 4.4 Special warnings and precautions for use and 4.2 Posology and Method of administration). No data are available for RASILEZ HCT in patients with severe renal impairment (creatinine clearance < 30 mL/min). However, as expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide. Therefore, RASILEZ HCT is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see 'CONTRAINDICATIONS').

CLINICAL TRIALS

Over 3,900 hypertensive patients received RASILEZ HCT once daily in clinical trials.

In hypertensive patients, once-daily administration of RASILEZ HCT provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks. The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. The antihypertensive effect of a single dose of the combination persisted for 24 hours. Upon withdrawal of the aliskiren treatment (aliskiren with or without hydrochlorothiazide add-on), the return of blood pressure towards baseline was gradual (3-4 weeks) with no evidence of the rebound effect.

RASILEZ HCT was studied in a placebo-controlled trials including 2,762 hypertensive patients with diastolic blood pressure ≥ 95 mmHg and < 110 mmHg (mean baseline blood pressure of 153.6/99.2 mmHg). In this study, RASILEZ HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg produced dose-dependent blood pressure reductions (systolic/diastolic) from 17.6/11.9 mmHg to 21.2/14.3 mmHg, respectively, compared to 7.5/6.9 mmHg with placebo. The greater blood pressure reductions with these combination doses were also significantly greater than the respective doses of aliskiren and hydrochlorothiazide when used alone. The combination of aliskiren and hydrochlorothiazide neutralised the reactive increase of PRA caused by hydrochlorothiazide.

When administered to patients with grade 2 hypertension (systolic BP 160-179 mmHg and diastolic BP 100-109 mm Hg), , RASILEZ HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg demonstrated significantly greater systolic/diastolic blood pressure control rates (< 140/90 mmHg) as compared to the respective monotherapies. In this population, RASILEZ HCT 150 mg/12.5 mg to 300 mg/25 mg provided dose-dependent systolic/diastolic blood pressure reduction from 20.6/12.4 mmHg to 24.8/14.5 mmHg, which were significantly superior to the respective monotherapies. The safety of the combination therapy was similar to the respective monotherapies regardless of severity of hypertension. Hypotension and related adverse events were uncommon with the combination treatment and, with no increased incidence in elderly patients.

In a study in 880 randomised patients not adequately responsive to aliskiren 300 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 15.8/11.0 mmHg, which were significantly greater than aliskiren 300 mg monotherapy. In a study in 722 randomised patients not adequately responsive to hydrochlorothiazide 25 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 16.78/10.7 mmHg, which were significantly greater than hydrochlorothiazide 25 mg monotherapy.

In another clinical trial, the efficacy and safety of RASILEZ HCT were also assessed in 489 obese hypertensive patients who did not respond to hydrochlorothiazide 25 mg (baseline systolic/diastolic blood pressure 149.4/96.8 mmHg). In this difficult-to-treat population, RASILEZ HCT provided a blood pressure reduction (systolic/diastolic) of 15.8/11.9 mmHg compared to 15.4/11.3 mmHg for irbesartan/hydrochlorothiazide, 13.6/10.3 mmHg for amlodipine/hydrochlorothiazide and 8.6/7.9 mmHg for hydrochlorothiazide monotherapy, with similar safety to hydrochlorothiazide monotherapy.

INDICATIONS

Treatment of hypertension.
Treatment should not be initiated with these fixed dose combinations.

CONTRAINDICATIONS

- Hypersensitivity to any of the components of RASILEZ HCT and to other sulfonamide derived drugs;
- Pregnancy (see 'Use in Pregnancy');
- Severe hepatic impairment;
- Severe renal impairment (creatinine clearance <30 mL/min);
- Anuria;
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.
- History of Angioedema with aliskiren;
- Concomitant administration with cyclosporine, a highly potent P-gp inhibitor, and other potent P-gp inhibitors such as verapamil and quinidine (see 'PRECAUTIONS - Interactions with Other Drugs').

PRECAUTIONS

Serum electrolyte changes: Based on experience with the use of other substances that affect the renin-angiotensin system (RAS), concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) should be used with caution. Hypokalaemia has been reported during treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended. The renin-aldosterone link is mediated by angiotensin II, so with coadministration of aliskiren the reduction in serum potassium is less pronounced than observed under monotherapy with hydrochlorothiazide (see 'PRECAUTIONS – Interactions', and 'ADVERSE REACTIONS').

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals. Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hypokalaemia, hyponatraemia and hypochloraemic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Warning signs of fluid or electrolyte imbalance are dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with aliskiren may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH).

Conversely, due to the aliskiren component of RASILEZ HCT, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with RASILEZ HCT, risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Caution is required when co-administering potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes with RASILEZ HCT.

There is no evidence that RASILEZ HCT would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Sodium and/or volume depleted patients: In patients with marked volume- and/or salt-depletion (e.g. those receiving high doses of diuretics) symptomatic hypotension could occur after initiation of treatment with RASILEZ HCT. This condition should be corrected prior to administration of RASILEZ HCT, or the treatment should start under close medical supervision.

Angioedema: As with other agents acting on the renin-angiotensin system, angioedema has been reported rarely in patients treated with aliskiren. If angioedema occurs, RASILEZ HCT should be promptly discontinued and appropriate therapy and monitoring provided until

complete and sustained resolution of signs and symptoms has occurred. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to ensure patient airways should be provided.

Impaired renal function: When RASILEZ HCT is used in patients with impaired renal function, periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. There is no experience regarding the administration of RASILEZ HCT in patients who have recently undergone kidney transplantation. No dosage adjustment is necessary in patients with renal impairment whose GFR is ≥ 30 ml/min/1.73 m2. However, in patients with mild to moderate renal impairment (GFR ≥ 30 ml/min/1.73 m2 but < 60 ml/min/1.73 m2), RASILEZ HCT should be administered with caution.

As for other agents acting on the renin-angiotensin system, caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (eg. Due to blood loss, severe prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease or kidney disease. Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Renal artery stenosis: No data are available on the use of RASILEZ HCT in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. However, as with other agents acting on the renin-angiotensin system, there is an increased risk of renal insufficiency, including renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

Hepatic impairment: Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with Rasilez HCT in patients with hepatic impairment.

Systemic lupus erythematosus: Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances: Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may occur during thiazide therapy. To date,

no data are available from clinical studies that were specifically-designed to evaluate the safety of RASILEZ HCT in diabetic patients .
Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Heart failure: Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV). RASILEZ HCT should be used with caution in patients with heart failure due to limited clinical efficacy and safety data.

General: In the event of severe and persistent diarrhoea, RASILEZ HCT therapy should be stopped.
As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.
Hypersensitivity reactions to hydrochlorothiazide may occur, but are more likely in patients with a prior history allergy or bronchial asthma.such a history.

Excipients : RASILEZ HCT contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. RASILEZ HCT contains wheat starch. It is suitable for people with coeliac disease. Patients with wheat allergy (different from coeliac disease) should not take this medicine.

Effects on ability to drive and use machines: As with other antihypertensive agents, it is advisable to exercise caution when driving or operating machinery.

Genotoxicity: The combination of aliskiren and hydrochlorothiazide has not been tested for mutagenicity or clastogenicity.

Aliskiren

Aliskiren was negative in a series of assays for gene mutation, chromosomal damage and DNA damage.

Hydrochlorothiazide

Hydrochlorothiazide did not iduce gene mutation in bacteria or chromosome damage in mammalian cells in several in vitro and in vivo assays. However, positive results were obtained in a mammalian cell assay for gene mutation (mouse lymphoma cell assay) and in two other tests (sister chromatid exchange assay in Chinese hamster ovary cells and nondisjunction assay in Aspergillus nidu/ans).

Carcinogenicity: The combination of aliskiren and hydrochlorothiazide has not been tested for carcinogenicity.

Aliskiren

The carcinogenic potential of aliskiren was assessed in a 2-year rat study and a 6-month transgenic mouse study. There was no significant increase in the incidence of neoplastic lesions in mice given up to 1500 mg/kg/day PO (ER <1 based on AVC). Inflammatory and proliferative changes were observed in the lower gastro-intestinal tract at dietary doses of 750 or 1500 mg/kg/day in both mice and rats (ER <I and 3 based on AVC, respectively). One colonic adenoma and one caecal adenocarcinoma were found in two separate rats at the dietary dose of 1500 mg/kg/day (ER 3 based on AVe). These tumour incidences were not statistically significant although these tumours were considered relatively rare when compared to the historical controls. The low absorption and biliary excretion of aliskiren in rats resulted in high local concentrations in the gastrointestinal tract. The faecal concentration in rats treated with a dose of 1500 mg/kg/day for a month was about 57 fold higher than the human faecal concentration (mg/g) at the MRHD. Overall, the data suggests that these tumour incidences may not be clinical relevant.

Hydrochlorothiazide

Two-year feeding studies in mice and rats showed no evidence of carcinogenic potential for hydrochlorothiazide in female mice at doses up to approximately 600 mg/kg/day, or in male and female rats at doses up to approximately 100 mg/kg/day. However, there was equivocal evidence for hepatocarcinogenicity in male mice treated with hydrochlorothiazide at approximately 600 mg/kg/day.

Use in Pregnancy (Category D)

There is no clinical experience with the use of RASILEZ HCT in pregnant women.

Aliskiren

Aliskiren should not be used during pregnancy or in women planning to become pregnant. Physicians prescribing any agents acting on the RAAS (reninangiotensinaldosterone system) should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, RASILEZ HCT should be discontinued as soon as possible.

Drugs that act on the RAAS can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors (a specific

class of drugs acting on the RAAS). When pregnancy is detected, RASILEZ HCT should be discontinued as soon as possible.

The use of drugs that act directly on the RAAS during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydraminos has been reported, presumably resulting from decreased fetal renal function. Oligohydraminos in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus
arteriosis have also been reported, although it is not clear whether these occurrences were due to exposure to the drug, In addition. in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects.

Infants with histories of in utero exposure to renin inhibitor should be closely observed for hypotension. oliguria and hyperkalemia.

Aliskiren was not teratogenic when administered at matemotoxic oral doses of 543 mg/kg/day to rats or 90 mg/kg/day to rabbits. An embryofetal NOAEL was established in rats with an oral dose of 270 mg/kg/day and in rabbits with 90 mg/kg/day, equivalent to <1. and 4- fold the MRHD based on AUC, respectively. Post-natal development in rats was unaffected by oral doses up to 181 mg/kg/day (ER <1. based on AUC).

Hydrochlorothiazide

Intrauterine exposure to thiazide diuretics is associated with fetal or neonatal thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults.

Use in Lactation

RASILEZ HCT is not recommended during lactation. It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. Hydrochlorothiazide is excreted into breast milk. Because of the potential for adverse effects on the breast-fed infant, a decision should be made whether to discontinue breast-feeding or discontinue use of RASILEZ HCT, taking in account the importance of both the control of hypertension and breast-feeding to the mother and infant

Interactions with Other Drugs

RASILEZ HCT

Co-administration of aliskiren and hydrochlorothiazide does not cause meaningful changes in the steady-state pharmacokinetic exposure (AUC) and the maximum concentration (Cmax) of both components in healthy volunteers.

Medicinal products affecting potassium: The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of aliskiren. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium, corticosteroids, ACTH, salicylic acid derivatives). Conversely, based on experience with the use of other medicinal products that blunt the renin-angiotensin system (RAS), concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. Adequate monitoring of serum potassium in patients at risk is recommended.

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium is recommended when RASILEZ HCT is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

Aliskiren

Aliskiren has a low potential for clinically relevant interactions with medicinal products commonly used to treat hypertension or diabetes.

Compounds that have been investigated in clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, fenofibrate, pioglitazone, allopurinol, isosorbide- 5-mononitrate, ramipril and hydrochlorothiazide and no clinically significant interactions have been observed.

Co-administration of aliskiren with either valsartan (decrease of 28%), metformin (decrease of 28%), amlodipine (increase of 29%) or cimetidine (increase of 19%) resulted in between 20% and 30% change in C_{max} or AUC of aliskiren. Co-administration of aliskiren had no significant impact on atorvastatin, valsartan, metformin or amlodipine pharmacokinetics. As a result no dose adjustment for aliskiren or these co-administered medications is necessary.

Co-administration of irbesartan reduced aliskiren Cmax up to 50% after multiple dosing. Preliminary data suggest that irbesartan may decrease aliskiren AUC and Cmax. Digoxin bioavailability may be slightly decreased by aliskiren.

In experimental animals it has been shown that Pgp is a major determinant of aliskiren bioavailability. Inducers of Pgp (St John's wort, rifampicin) might therefore decrease the bioavailability of aliskiren.

CYP 450 interactions: At expected therapeutic concentrations aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and CYP3A). Aliskiren does not induce CYP3A4. Aliskiren is metabolised minimally by the cytochrome P450 enzymes CYP3A4, CYP3A5, and CYP2D6, therefore aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce, or are metabolised by these enzymes.

P glycoprotein interactions: *In vitro* studies indicate that MDR1 (Pgp) was found to be the major efflux transporter system involved in absorption and disposition of aliskiren.. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter.

Pgp substrates or weak inhibitors: No relevant interactions with atenolol, digoxin, amlodipine, and cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by 50%.

Pgp moderate inhibitors: Co-administration of ketoconazole (200 mg) with aliskiren (300 mg) resulted in a 80% increase in plasma levels of aliskiren (AUC and C_{max}). Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Co-administration of a single oral dose of 300 mg aliskiren with 240 mg verapamil increased AUC and Cmax of aliskiren by ~2-fold. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. As a result no dose adjustment for aliskiren is necessary.

Potent Pgp potent inhibitors: A single dose drug interaction study in healthy subjects has shown that cyclosporin A (200 and 600 mg) increases Cmax of aliskiren 75 mg by approximately 2.5 fold and the AUC by approximately 5-fold. Therefore, the concomitant use of both drugs is contraindicated.

Furosemide: When aliskiren was co-administered with frusemide, the AUC and Cmax of furosemide were reduced by 28% and 49% respectively. It is therefore recommended that the effects be monitored when initiating and adjusting frusemide therapy to avoid possible under-utilisation in clinical situations of volume overload.

Non-steroidal anti-inflammatory drugs (NSAIDs): As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients)

aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination of aliskiren with an NSAID requires caution, especially in elderly patients.

Potassium and potassium sparing diuretics: Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of aliskiren with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other substances that may increase serum potassium levels (e.g. heparin) may lead to increases in serum potassium. If co-medication is considered necessary, caution is advisable (see 'ADVERSE REACTIONS').

Warfarin: The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

Food intake: Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially.

Hydrochlorothiazide

Lithium: Should not generally be given with diuretics. Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazides. There is no experience with concomitant use of aliskiren and lithium. Therefore, monitoring of serum lithium concentrations is recommended during concurrent use.

Curare derivatives: Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.

Non-steroidal anti-inflammatory drugs: Concomitant administration of NSAIDs (e.g. salicylic acid derivative, indomethacin) may weaken the diuretic and antihypertensive activity of the thiazide component of RASILEZ HCT. Concurrent hypovolaemia may induce acute renal failure.

Medicinal products affecting potassium: The hypokalaemic effect of diuretics may be increased by kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives.

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesemia may occur as unwanted effects, favouring the onset of digitalis-induced cardiac arrhythmias.

Antidiabetic medicinal products: It may prove necessary to readjust the dosage of insulin and of oral antidiabetic agents.

Anticholinergic agents: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.

Methyldopa: There have been reports in the literature of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Cholestyramine: Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine.

Vitamin D and calcium salts: Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

Cyclosporin: Concomitant treatment with cyclosporin may increase the risk of hyperuricaemia and gout-type complications.

Carbamazepine: Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatraemia. Such patients should therefore be advised about the possibility of hyponatraemic reactions, and should be monitored accordingly.

Other interactions: Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol, may increase the risk of adverse effects caused by amantadine, may enhance the hyperglycaemic effect of diazoxide, and may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

ADVERSE EFFECTS

The safety of RASILEZ HCT has been evaluated in 9 clinical trials with more than 3900 patients, including over 700 treated for over 6 months, and 190 for over 1 year. The incidence of adverse events showed no association with gender, age, body mass index, race or ethnicity. Treatment with RASILEZ HCT had an overall incidence of adverse experiences at doses up to 300 mg/25 mg similar to placebo. Adverse events have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most frequent adverse drug reaction with aliskiren/hydrochlorothiazide is diarrhoea.

Table 1 Number (%) of patients with most frequent Adverse Events (> 2% for any group) by preferred term (in short term, double-blind all controlled studies) (safety population).

Preferred term	Placebo N=193 n (%)	Aliskiren N=973 n (%)	HCTZ N=1075 n (%)	Aliskiren/HCTZ 150/12.5 mg N=184 n (%)	Aliskiren/HCTZ 150/25 mg N=719 n (%)	Aliskiren/HCTZ 300/12.5 mg N=474 n (%)	Aliskiren/HCTZ 300/25 mg N=1030 n (%)
Any adverse experience	**85 (44.0)**	**312 (32.1)**	**420 (39.1)**	**72 (39.1)**	**228 (31.7)**	**135 (28.5)**	**297 (28.8)**
Headache	26 (13.5)	56 (5.8)	61 (5.7)	15 (8.2)	21 (2.9)	22 (4.6)	28 (2.7)
Nasopharyngitis	10 (5.2)	25 (2.6)	42 (3.9)	3 (1.6)	22 (3.1)	9 (1.9)	28 (2.7)
Dizzines	2 (1.0)	6 (0.6)	21 (2.0)	6 (3.3)	10 (1.4)	12 (2.5)	17 (1.7)
Influenza	3 (1.6)	12 (1.2)	9 (0.8)	1 (0.5)	10 (1.4)	4 (0.8)	12 (1.2)
Diarrhoea	1 (0.5)	14 (1.4)	20 (1.9)	1 (0.5)	10 (1.4)	10 (2.1)	8 (0.8)
Back pain	5 (2.6)	10 (1.0)	14 (1.3)	2 (1.1)	6 (0.8)	5 (1.1)	10 (1.0)
Arthralgia	1 (0.5)	7 (0.7)	11 (1.0)	1 (0.5)	6 (0.8)	4 (0.8)	7 (0.7)
Bronchitis	3 (1.6)	11 (1.1)	10 (0.9)	4 (2.2)	4 (0.6)	4 (0.8)	7 (0.7)
Cough	1 (0.5)	5 (0.5)	10 (0.9)	2 (1.1)	7 (1.0)	2 (0.4)	6 (0.6)
Vertigo	1 (0.5)	6 (0.6)	7 (0.7)	1 (0.5)	4 (0.6)	5 (1.1)	12 (1.2)
Nausea	4 (2.1)	4 (0.4)	10 (0.9)	2 (1.1)	5 (0.7)	3 (0.6)	4 (0.4)
Asthenia	0 (0.0)	8 (0.8)	7 (0.7)	1 (0.5)	3 (0.4)	3 (0.6)	4 (0.4)
Fatigue	2 (1.0)	6 (0.6)	13 (1.2)	1 (0.5)	4 (0.6)	2 (0.4)	6 (0.6)
Oedema peripheral	1 (0.5)	11 (1.1)	13 (1.2)	2 (1.1)	2 (0.3)	3 (0.6)	5 (0.5)
Sinusitis	1 (0.5)	3 (0.3)	1 (0.1)	1 (0.5)	4 (0.6)	3 (0.6)	2 (0.2)
Vomiting	4 (2.1)	1 (0.1)	5 (0.5)	3 (1.6)	4 (0.6)	0 (0.0)	1 (0.1)
Flatulence	1 (0.5)	4 (0.4)	4 (0.4)	0 (0.0)	1 (0.1)	1 (0.2)	2 (0.2)
Angina pectoris	0 (0.0)	1 (0.1)	2 (0.2)	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)
Myocardial infarction	0 (0.0)	0 (0.00	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Tendonitis	0 (0.0)	4 (0.4)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)

N=number of patients, n=number with AEs, %=(n/N)*100.

Additional information on the combination

Diarrhoea: Diarrhoea is a dose-related adverse drug reaction for aliskiren. Doses above aliskiren 300 mg did not give an increased blood pressure response but increased the rate of diarrhoea. In controlled clinical trials, the incidence of diarrhoea in RASILEZ HCT treated patients was low and not more than that in aliskiren or hydrochlorothiazide treated patients.

Serum potassium: In a large placebo-controlled clinical trial, the opposing effects of aliskiren (150 mg or 300 mg) and hydrochlorothiazide (12.5 mg or 25 mg) on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant.

Periodic determinations of serum potassium to detect possible electrolyte imbalance should be performed at appropriate intervals.

Additional information on individual components

Adverse reactions previously reported with one of the individual components may occur with RASILEZ HCT even if not observed in clinical trials.

Aliskiren

Treatment with aliskiren was well tolerated with an overall incidence of adverse experiences similar to placebo up to 300 mg. Adverse events have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common adverse drug reaction is diarrhoea. Other adverse drug reactions that occurred during treatment with aliskiren include rash and angioedema. In controlled clinical trials, angioedema occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or hydrochlorothiazide. In the event of any signs suggesting an allergic reaction (in particular difficulties in breathing, or swallowing, or swelling of the face, extremities, eyes, lips and/or tongue) patients should discontinue treatment and contact the physician. The incidence of cough was similar in placebo (0.6%) and aliskiren treated (0.9%) patients.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/L and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other agents acting on the renin-angiotensin system, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers. These decreases led to slight increases in rates of anaemia with aliskiren compared to placebo (0.1% for any aliskiren use vs 0% for placebo).

Serum potassium: Increases in serum potassium were minor and infrequent in patients with essential hypertension treated with aliskiren alone (0.9% compared to 0.6% with placebo). However, in one study where aliskiren was used in combination with an angiotensin converting enzyme inhibitor (ACEI) in a diabetic population increases in serum potassium were more frequent (5.5%). Therefore as with any agent acting on the RAS system, routine monitoring of electrolytes and renal function is indicated in the diabetic population and those with kidney disease and heart failure when using aliskiren.

Hydrochlorothiazide

Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in RASILEZ HCT. The following adverse experiences have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide irrespective of their causal association with the study drug:

Electrolyte and metabolic disorders (see 'PRECAUTIONS').

Common: Urticaria and other forms of rash, loss of appetite, mild nausea and vomiting, postural hypotension, which may be aggravated by alcohol, anaesthetics or sedatives, and impotence.

Rare: Photosensitisation, abdominal distress, constipation, diarrhoea, and gastrointestinal discomfort, intrahepatic cholestasis or jaundice, cardiac arrhythmias, headache, dizziness or lightheadedness, sleep disturbances, depression, paraesthesia, disturbances of vision, and thrombocytopenia, sometimes with purpura.

Very rare: Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, pancreatitis, leukopenia, agranulocytosis, bone marrow depression, haemolytic anaemia, hypersensitivity reactions, respiratory distress including pneumonitis and pulmonary oedema.

DOSAGE AND ADMINISTRATION

The dose of RASILEZ HCT must be determined by careful titration of the dose of each of the individual components. The recommended dose is one tablet per day, one of Rasilez HCT 150/12.5 or Rasilez HCT 150/25 or Rasilez HCT 300/12.5 or Rasilez HCT 300/25 mg. The maximum recommended dose of the combination therapy is 300/25 mg once daily.

The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.

Patients should establish a routine pattern for taking RASILEZ HCT with regard to meals. RASILEZ HCT should be taken with light meals. Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially.

Patients not adequately treated on monotherapy

A patient whose blood pressure is not adequately controlled on monotherapy may be switched to the combination therapy with RASILEZ HCT. When clinically appropriate direct change from monotherapy to RASILEZ HCT fixed combination may be considered.

Patients adequately treated with separate tablets of Aliskiren and Hydrochlorothiazide

For convenience, patients already receiving aliskiren and hydrochlorothiazide from separate tablets may be switched to a single tablet of RASILEZ HCT containing the same component doses.

Renal impairment: No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see 'PRECAUTIONS - Impaired renal function' and 'PHARMACOLOGY – Pharmacokinetics'). Due to the hydrochlorothiazide component, RASILEZ HCT is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see 'CONTRAINDICATIONS' and 'PHARMACOLOGY – Pharmacokinetics').

Hepatic impairment: No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment (see 'PHARMACOLOGY – Pharmacokinetics'). Due to the hydrochlorothiazide component, RASILEZ HCT is contraindicated in patients with severe hepatic impairment (see 'CONTRAINDICATIONS').

Use in elderly patients (over 65 years): No initial dosage adjustment is required for elderly patients.

Use in children and adolescents: The safety and efficacy of RASILEZ HCT has not been established in children and adolescents (below 18 years of age) and therefore RASILEZ HCT is not recommended in this population.

OVERDOSAGE

No data are available related to overdose in humans. The most likely manifestations of overdosage would be hypotension, related to the antihypertensive effect of aliskiren and hydrochlorothiazide. If symptomatic hypotension should occur, supportive treatment should be initiated.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

RASILEZ HCT 150/12.5: White, biconvex, ovaloid film-coated tablet imprinted with LCI on one side and NVR on the other side. Packs of 7, 14, 28, 30, 49, 50, 56, 90, 98, and 280.

RASILEZ HCT 150/25: Pale yellow, biconvex, ovaloid film-coated tablet imprinted with CLL on one side and NVR on the other side. Packs of 7, 14, 28, 30, 49, 50, 56, 90, 98, and 280.

RASILEZ HCT 300/12.5: Violet white, biconvex ovaloid film-coated tablet imprinted with CVI on one side and NVR on the other side. Packs of 7, 14, 28, 30, 49, 50, 56, 90, 98, and 280.

RASILEZ HCT 300/25: Light yellow, biconvex, ovaloid film- coated tablet imprinted with CVV on one side and NVR on the other side. Packs of 7, 14, 28, 30, 49, 50, 56, 90, 98, and 280.

Not all pack sizes may be marketed.

Storage: Keep in the original package. Store below 30°C. Protect from moisture. Protect from light.

Poisons schedule: S4

SPONSOR

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DATE OF APPROVAL

Approved by the Therapeutic Goods Administration: 4 February 2010

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rah280110i.doc based on the CDS of 22 November 2007, the Non-clinical (15/04/09) and clinical (01/05/09) recommendations and Novartis response to the CER dated 30 May 2009 an d to S31 No. 2008-2072-3-pce-5 dated 02 September 2009 and the Delegate's Overview dated 23 October 2009 and email dated 27/01/10.