Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Aliskiren/Amlodipine

Proprietary Product Name: Rasilamlo

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

August 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Fixed Combination
Decision:	Approved
Date of Decision:	10 June 2011
Active ingredient(s):	Aliskiren/Amlodipine
Product Name(s):	Rasilamlo
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 Aliskiren/5 mg amlodipine, 150 mg Aliskiren/10 mg amlodipine, 300 mg Aliskiren/5 mg amlodipine, 300 mg Aliskiren/10 mg amlodipine
Container(s):	Blister packs
Pack size(s):	7, 14, 28, 30 and 56 tablets
Approved Therapeutic use:	Rasilamlo is indicated for the treatment of hypertension. Treatment should not be initiated with these fixed dose combinations.
Route(s) of administration:	Oral
Dosage:	The recommended dose is one tablet per day, one of Rasilamlo 150/5 or Rasilamlo 150/10 or Rasilamlo 300/5 or Rasilamlo 300/10. The maximum recommended dose of the combination therapy is 300/10 mg once daily.
ARTG Number (s):	170431, 170434, 170435, 170436

Product Background

This AusPAR describes the evaluation of an application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register new fixed dose combinations of aliskiren hemifumarate and amlodipine besylate (Rasilamlo).[1]

Rasilez and Enviage (aliskiren) 150 mg and 300 mg tablets are registered on the Australian Register of Therapeutic Goods (ARTG) (entry date 23 June 2008). Rasilez HCT and Enviage HCT, aliskiren in combination with hydrochlorothiazide, were added to the ARTG on 7 April 2010 in dose combinations 150/25 mg, 300/25 mg, 150/12.5 mg and 300/12.5 mg.[2] Both Rasilez /Enviage and Rasilez HCT/ Enviage HCT are indicated for the treatment of hypertension. These products are also sponsored by Novartis Pharmaceuticals Pty Ltd.

[1] Aliskiren hemifumarate and amlodipine besylate will be referred to simply as aliskiren and amlodipine respectively for the remainder of this AusPAR.

[2] TGA. AusPAR for Aliskiren (as hemifumarate)/hydrochlorothiazide, March 2010, available at: http://www.tga.gov.au/pmeds/auspar/auspar-rasilez.pdf

Amlodipine has been registered in Australia for many years. It is available as 5 mg and 10 mg tablets. On the ARTG there are many generics and also many fixed combination products containing amlodipine. Amlodipine is indicated in the treatment of hypertension and also in the treatment of chronic stable angina. Novartis Pharmaceuticals Pty Ltd is not a sponsor of amlodipine alone in Australia but sponsors an amlodipine/valsartan combination product (Exforge/Ejocia).[3]

Aliskiren and amlodipine have a combined effect on blood pressure by acting on different but complementary systems of blood pressure regulation. Aliskiren is a direct inhibitor of renin and therefore inhibits the renin-angiotensin system. Amlodipine is a long acting calcium channel blocker resulting in vascular smooth muscle relaxation and subsequent reduced peripheral vascular resistance and blood pressure.

Regulatory Status

A similar application was approved in the USA in 27 August 2010 and in the European Union (EU) on 18 February 2011. The indication in the US for Tekamlo is:

For treatment of hypertension

- *for initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals;*
- *in patients not adequately controlled with monotherapy;*
- *as a substitute for its titrated components.*

The indication for Rasilamlo in the EU is:

For the treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled with aliskiren or amlodipine used alone.

A similar application was submitted in Canada on 15 December 2010.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

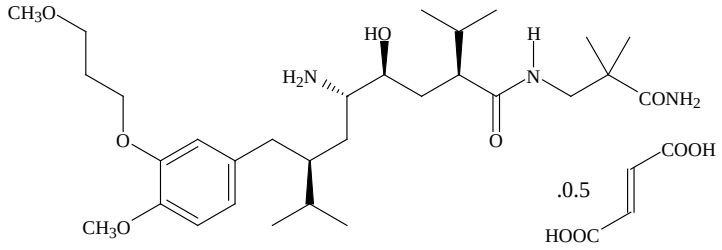
Drug Substances (active ingredients)

There are European, British and US pharmacopoeial monographs for amlodipine but there are no compendial monographs for aliskiren hemifumarate or aliskiren products. The details relating to aliskiren drug substance are the same as for the registered products. The amlodipine used in the products is covered by European Directorate of Quality Medicines Certificates of Suitability certifying that the material meets the European monograph for amlodipine.

Structures and other details of the drug substances are shown in Figure 1.

Figure 1: Structure and chemical details for aliskiren and amlodipine

[3] TGA. AusPAR for Amlodipine/Valsartan, October 2010. Available at: http://www.tga.gov.au/pmeds/auspar/auspar-exforge-ejo.pdf



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

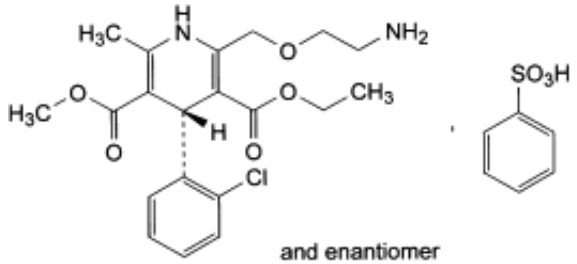
CAS Number: [173334-58-2] ([173334-57-1] for free base)

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



amlodipine besylate

Chemical Name:
3-ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate

CAS Number: [111470-99-6] ([88150-42-9] for free base)

Molecular Formula: $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$

Molecular Weight: 567.1 (408.9 for free base)

Description: A white to almost white powder

Solubility in water: Slightly soluble (1.0-10 mg/mL, 0.1-1.0%)

Drug Product

The tablets are to be manufactured using separate aliskiren and amlodipine granulations. These are then mixed, compressed, film coated and packed.

The tablets contain no unusual excipients and the quality of the excipients is adequately controlled. No material of animal origin is used.

The cores of the "300/10" and "150/5" tablets are direct scales. The cores of the "150/10' and "150/5" tablets have the amount of microcrystalline cellulose adjusted to compensate for the different mass of amlodipine besylate present. A similar adjustment is made to the cores of the "300/10' and "300/5" tablets.

All the tablets are the same shape (ovaloid convex) with those containing 150 mg of aliskiren being 16 x 6.3 mm and those containing 300 mg aliskiren being 21 x 8.3 mm. The

film-coats of the different strengths are different shades of yellow or brown so that the tablets can be distinguished. The tablets are distinguished by markings ("T2", "T7", "T11", "T12"). They are further distinguished by the packaging which is a different colour for each strength (yellow, green, red and blue) and clearly marks each strength. None of the tablets are scored.

The tablets are well controlled with satisfactory expiry limits and release limits that allow for the changes observed on storage.

The limits for four specified degradants of aliskiren are higher than accepted for the monotherapy tablets and also above the International Council on Harmonisation (ICH) qualification threshold of 0.2%.[4] However data were included in the nonclinical section to support the proposed limits.

One degradant of amlodipine is limited to the ICH qualification threshold of 0.5%. This limit is also allowed by the US monograph.

Compared to monotherapy tablets a new degradant was observed. The proposed expiry limit was above the ICH qualification threshold of 0.5%. However data was included in the nonclinical section to support the proposed limit. This degradant increased in a more than linear fashion on storage and a release limit has been set to allow for the increase. The limits for an unidentified degradant meet the ICH identity threshold.

Given that alcohols are used in the aliskiren granulate the formation of benzene sulfonates is theoretically possible and the sponsor has included limits for each of these.

Stability data was provided to support the proposed shelf lives of 9 months when stored below 30ºC in opaque PA/Al/PVC // Al blister packs. The storage condition 'protect from moisture' is also used. Data was also provided to support that the tablets may be stored in bulk for a maximum of 3 months before packaging in the proposed blister packs.

Bioavailability

Clinical Background

The Phase III clinical efficacy studies were performed using the concomitant administration of monotherapy aliskiren tablets (as registered in Australia) and monotherapy amlodipine tablets (German 5 mg Norvasc tablets).

Studies submitted

The sponsor submitted four bioavailability studies, one pharmacokinetic interaction study, a justification for not generating bioavailability data using two of the tablet strengths (150/10 and 150/5) and a justification for using the German 5 mg Norvasc comparator.

The test methods used in the studies to determine levels of aliskiren and amlodipine in subjects' plasma samples were evaluated and found to give accurate and precise results. The subject samples were collected at appropriate times to allow good estimation of the pharmacokinetic parameters including the maximal plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC).

Study CSPA100A2101 (Bioequivalence)

This was a single dose, five way crossover study in 60 healthy subjects (46 completed) to compare the proposed 300/10 fixed dose combination (FDC) tablet (and three other FDC

[4] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

tablets) to the concomitant administration of the monotherapies. Given the presence of study CSPA100A2102 which used more subjects, the results of this study were accepted without evaluation. The results showed bioequivalence for both aliskiren and amlodipine responses (Table 1).

Table 1: Comparison of pharmacokinetic parameters for the FDC and separate components in Study CSPA100A2101

Parameter	Geometric Mean Ratio (FDC/Separate) and [90% Confidence Intervals]	
	Aliskiren	Amlodipine
AUC_{0-t}	0.96 [0.87-1.05]	1.01 [0.98-1.05]
Cmax	0..96 [0.82-1.13]	1.03 [1.00-1.07]

Study CSPA100A2102 (Bioequivalence)

This was a single dose, two way crossover study in 120 healthy subjects (112 completed) to compare the proposed 300/10 fixed dose combination (FDC) tablet to the concomitant administration of the monotherapies (registered 300 mg aliskiren tablet and 2 x German 5 mg Norvasc tablets). Bioequivalence was demonstrated for both aliskiren and amlodipine responses (Table 2).

Table 2: Comparison of pharmacokinetic parameters for the FDC and separate components in Study CSPA100A2102

Parameter	Geometric Mean Ratio (FDC/Separate) and [90% Confidence Intervals]	
	Aliskiren	Amlodipine
AUC_{0-t}	0.96 [0.89-1.03]	0.97 [0.95-0.99]
Cmax	0.95 [0.85-1.07]	0.97 [0.95-1.00]

Study CSPA100A2103 (Bioequivalence)

This was a single dose, two way crossover study in 120 healthy subjects (109 completed) to compare the proposed 150/10 FDC tablet to the concomitant administration of the monotherapies (registered 150 mg aliskiren tablet and 2 x German 5 mg Norvasc tablets). Bioequivalence was demonstrated for both aliskiren and amlodipine responses (Table 3).

Table 3: Comparison of pharmacokinetic parameters for the FDC and separate components in Study CSPA100A2103

Parameter	Geometric Mean Ratio (FDC/Separate) and [90% Confidence Intervals]	
	Aliskiren	Amlodipine
AUC_{0-t}	0.97 [0.90-1.04]	0.99 [0.95-0.99]
Cmax	0.99 [0.88-1.12]	0.98 [0.96-1.01]

Study CSPA100A2104 (Food Effect)

This was a single dose, two way crossover study in 36 healthy subjects (35 completed) to determine the effect of food on the bioavailability of aliskiren and amlodipine from the proposed tablets (the 300/10 tablet was used).The results (Table 4) indicate:

- An 80% decrease in aliskiren levels with food. T_{max} was also reduced from 3 to 1.5 hours (h).
- No change in amlodipine levels (or T_{max}) with food.

Table 4: Comparison of pharmacokinetic parameters for fed and fasted patients

Parameter	Geometric Mean Ratio (Fed/Fasted) and [90% Confidence Intervals]	
	Aliskiren	Amlodipine
AUC_{0-t}	**0.20** [**0.18-0.23**]	1.03 [0.97-1.08]
Cmax	**0.10** [**0.08-0.12**]	1.02 [0.97-1.07]

Study CSPA100A2218 (Interaction)

This was a three way sequential, steady state study to compare the pharmacokinetic interactions of aliskiren and amlodipine at steady state in 24 subjects using the registered 300 mg aliskiren tablet and a German 10 mg Norvasc tablet. These results indicate:

- A 29% increase in aliskiren levels in the presence of amlodipine (90% confidence intervals (CIs) for C_{max} = 0.83-1.69 and the area under the plasma concentration time curve for a dosing period (AUC_{0-t}) = 1.07-1.55).
- No difference the amlodipine levels indicating no interaction with aliskiren (90% CIs for C_{max} = 0.93-1.05 and AUC_{0-t} = 0.92-1.05).

The sponsor argued that these results are not statistically significant due to the large intra-subject variability of aliskiren.

Justifications for Not Performing Bioavailability Studies

Other Strengths

A justification was provided for not providing bioavailability data comparing the 150/5 and 300/5 strength FDC tablets to the monotherapies used in the Phase III clinical efficacy studies. The chemistry aspects of this justification were accepted. The dissolution profile results of all four strengths at pH 1, 4.5 and 6.8 were similar.

Overseas Reference Product

No data were included comparing an Australian registered amlodipine tablet to the German Norvasc amlodipine tablets used in the Phase III clinical efficacy studies and bioequivalence studies. The chemistry aspects of this justification were acceptable. It was also noted that at the proposed maximum daily dose (10 mg), amlodipine can be considered BCS Class 1 and that this justification has been accepted previously in relation to other FDC tablets of Novartis containing amlodipine.[5]

The Delegate was asked to decide whether the clinical aspects in relation to the justifications for not providing bioavailability data were acceptable.

[5] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Consideration by the Advisory Committee

Details of this submission were presented at the 136th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) in January 2011. The PSC:

- Considered the justifications for not providing bioavailability data on all strengths of the fixed dose combination tablets and for using an overseas formulation of amlodipine tablets in the clinical and bioavailability studies were acceptable.
- Agreed that the Delegate should be informed of the magnitude to the effect of food on the bioavailability of aliskiren and the possibility of an interaction on the aliskiren response by amlodipine.
- Raised an objection to the use of multiple trade names for the same products.

Quality Summary and Conclusions

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

In relation to bioavailability:

- Data have been provided to demonstrate that the proposed fixed dose combination tablets can be a replacement therapy in patients already receiving aliskiren and amlodipine from separate tablets.
- Food (high fat meal) reduces the bioavailability of aliskiren (but not amlodipine). However one statement in the PI states the tablets can be taken without respect to food and another that the tablets should be taken with a light meal.
- There is possibly a slight interaction on the aliskiren response by amlodipine.
- The justifications for not providing bioavailability data were acceptable with respect to chemistry aspects and were referred to the Delegate with respect to clinical aspects.

III. Nonclinical Findings

Introduction

The proposed fixed combination contains approved compounds indicated for long term use and although the pharmaco-toxicological profiles of the individual components have been previously well characterized, clinical experience with concomitant use of the combination is lacking. This highlights the importance of nonclinical bridging studies, particularly given that both aliskiren and amlodipine exert their actions on the cardiovascular system, and that renal (aliskiren and amlodipine) and cardiac toxicities (amlodipine) have been identified for the individual medicines in nonclinical studies previously evaluated by the TGA.

The sponsor submitted a bridging data package consisting of 2 week and 13 week oral (PO) repeat dose toxicity studies in rats (including toxicokinetics) plus *in vitro* tests of mutagenicity and chromosomal aberration. The test item in all studies was a special batch of aliskiren/amlodipine combined at the clinically intended ratio (30:1) that contained additional amounts of an amlodipine related degradation product (NAP 010-07). The latter was added in order to qualify this impurity at the proposed expiry limit of 1.7% (based on amlodipine content).

All studies except for the 2 week dose range finding study were Good Laboratory Practice (GLP) compliant.

The potential of the combination to cause pharmacodynamic or specific pharmacokinetic interactions was not tested. Appropriate justifications were provided for the absence of such studies (see separate sections below).

No studies of carcinogenicity or reproductive toxicity were performed with the combination as these areas have been thoroughly evaluated for both aliskiren and amlodipine and currently available clinical data do not raise any specific safety concerns in these areas.

Overall, the submitted nonclinical data package was consistent with the TGA-adopted EU guidelines on the nonclinical development of fixed combinations of medicinal products.[6]

Pharmacology

Efficacy and pharmacodynamic (PD) interactions

The absence of nonclinical PD studies with the combination was justified by the sponsor on the basis of a lack of appropriate animal PD models as well as consideration of the large amount of experimental and clinical data showing greater blood pressure reductions (than monotherapy) of combinations of calcium channel blockers (CCB) and blockers of the renin-angiotensin aldosterone system (RAAS) such as ACE inhibitors or angiotensin receptor blockers (ARBs).

Existing animal models for investigating the PD of the combination would be expected to be dominated by either the aliskiren component (for example in double transgenic mice that over express human genes for renin and angiotensinogen) or the amlodipine component (for example in normal rats where aliskiren has weak potency of aliskiren against rat renin).

On balance, the absence of nonclinical efficacy data is reasonable given the existing clinical data for the efficacy of CCB/RAAS blockers, and the likelihood that aliskiren will additionally inhibit the well know compensatory rise in plasma renin activity that normally accompanies RAAS blockade by ACE inhibitors and ARBs. Moreover, the potential for unexpected PD interactions is unlikely given the separate and distinct mechanism of action of each component.

Pharmacokinetics

Pharmacokinetic (PK) interactions

The pharmacokinetic profiles of both aliskiren and amlodipine have been previously evaluated by the TGA and comprehensive data obtained in both animals and humans have been published in the literature.

Potential interactions at the oxidative metabolism level are unlikely as aliskiren is primarily eliminated by biliary efflux via MDR1 whereas amlodipine undergoes extensive metabolism, mostly mediated by cytochrome P450 (CYP) 3A4.

Toxicokinetic data from the 13 week toxicity study in rats failed to reveal any significant differences between the PK of the individual drugs in combination versus the individual drugs alone (Table 5).

Clinical data showed no relevant drug-drug interactions between aliskiren and amlodipine when investigated in free combination as part of the previous evaluation of aliskiren.

[6] EMEA, Committee for Medicinal products for Human Use (CHMP), 24 January 2008. Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products, CHMP/SWP/258498/2005.

Relative exposure

The systemic exposure levels of aliskiren and amlodipine were measured in both 2 week and 13 week oral toxicity studies in rats dosed with the combination.

Relative exposure estimates for both compounds have been normalised according to the free fraction of the drug in rats and humans (Table 5).

Table 5: Relative exposure to aliskiren and amlodipine in rat PO repeat dose toxicity studies

Species/study number	Oral dose aliskiren/ amlodipine (mg/kg/day)	Sex	$AUC_{0\text{-}24h}$ (ng.h/mL)	C_{max} (ng/mL)	Free $AUC_{0\text{-}24h}$ (ng.h/mL)	Free C_{max} (ng/mL)	Unbound Exposure Ratio	
							AUC	C_{max}
ALISKIREN								
13 week rat (study 0670747)	0/10	♂	-	-	-	-	-	-
		♀	-	-	-	-	-	-
2 week rat (study 0670746)	30/1 (**NOAEL**)	♂	177	49.2	110	31	**0.1**	1.8
		♀	111	24.1	69	15	**0.1**	0.9
13 week rat (study 0670747)	30/1	♂	47.8	4.4	30	3	0.02	0.2
		♀	67.4	20.8	42	13	0.03	0.8
13 week rat (study 0670747)	90/3 (**NOAEL**)	♂	331	39.2	205	24	**0.2**	1.4
		♀	457	299	283	185	**0.2**	11.0
2 week rat (study 0670746)	100/3	♂	311	63.4	193	39	0.2	2.3
		♀	771	189	478	117	0.4	7.0
13 week rat (study 0670747)	300/0	♂	964	187	598	116	0.5	6.9
		♀	1770	227	1097	141	0.9	8.4
2 week rat (study 0670746)	300/10	♂	1330	201	825	125	0.7	7.4
		♀	3510	299	2176	185	1.8	11.0
13 week rat (study 0670747)	300/10	♂	1040	114	645	71	0.5	4.2
		♀	1410	214	874	133	0.7	7.9
Human (study CSPP100A2218, day 49)	300/10 mg once a day for 14 days.	-	2470	33.6	1235	17	-	-

Species/study number	Oral dose aliskiren/ amlodipine (mg/kg/day)	Sex	$AUC_{0\text{-}tlast}$ (ng*h/mL)	C_{max} (ng/mL)	Free $AUC_{0\text{-}24h}$ (ng.h/mL)	Free C_{max} (ng/mL)	Unbound Exposure Ratio	
							AUC	C_{max}
AMLODIPINE								
13 week rat (study 0670747)	0/10	♂	3650	264	3541	256	7.8	17.5
		♀	4610	358	4472	347	9.8	23.8
2 week rat (study 0670746)	30/1 (**NOAEL**)	♂	97.7	13.4	95	13	**0.2**	0.9
		♀	109	18.3	106	18	**0.2**	1.2
13 week rat (study 0670747)	30/1	♂	154	12.3	149	12	0.3	0.8
		♀	167	15.6	162	15	0.4	1.0
13 week rat (study 0670747)	90/3 (**NOAEL**)	♂	594	61	576	59	**1.3**	4.1
		♀	850	81.2	825	79	**1.8**	5.4
2 week rat (study 0670746)	100/3	♂	420	31.6	407	31	0.9	2.1
		♀	435	33.4	422	32	0.9	2.2
13 week rat (study 0670747)	300/0	♂	-	-	-	-	-	-
		♀	-	-	-	-	-	-
2 week rat (study 0670746)	300/10	♂	2410	157	2338	152	5.1	10.4
		♀	2150	137	2086	133	4.6	9.1
13 week rat (study 0670747)	300/10	♂	3990	287	3870	278	8.5	19.1
		♀	3710	256	3599	248	7.9	17.0
Human (study CSPP100A2218, day 49	300/10 mg once a day for 14 days.	-	466	14.9	457	15	-	-

% plasma protein binding for aliskiren was 38% in rats and 50% in humans;
% plasma protein binding for amlodipine was 3% in rats and 2% in humans (Stopher et al 1988, Meredith et al 1992).[7,8]
NOAEL: No Observable Adverse Effect Level
♂: male, ♂: female

Exposure to aliskiren after single or multiple doses and to amlodipine after a single dose were generally dose proportional following administration of the drug combination. Exposure ratios for aliskiren and amlodipine at the No Observable Adverse Effect Level (NOAEL) in both the 2 and 13 week rat toxicity studies were similar to, or less than, the exposure anticipated clinically at the Maximum Recommended Human Dose (MRHD) of 300/10 mg aliskiren/amlodipine.

[7] Stopher DA, Beresford AP, Macrae PV, Humphrey MJ. The metabolism and pharmacokinetics of amlodipine in humans and animals. J Cardiovasc Pharmacol 1988; 12: S55-S59.
[8] Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. Clin Pharmacokinet 1992; 22: 22-31.

Toxicology

Toxicity was observed at the highest doses used in the 13 week study in the heart and adrenal glands at the aliskiren exposures of 0.5 (male) to 0.7 (female) and amlodipine exposures of 8.5 (male) to 7.9 (female)

Toxicological interactions

The selection of the rat for the combination toxicology studies was appropriate as previous applications have thoroughly characterised the PD, PK and toxicology of the individual components in this species. High dose selections for the 2 week and 13 week toxicity studies (300/10 mg/kg/day) were based on the results of previous toxicity data with aliskiren and amlodipine and were considered to be at, or above, the maximum tolerated dose for this species.

Previous toxicology evaluations found that aliskiren caused gastrointestinal effects in rats due to low absorption after oral administration (high local exposure), as well as haematological effects and renal effects, probably due to exaggerated pharmacological activity.

As monotherapy, the toxicity profile of amlodipine in rats has previously been shown to include hypertrophy (zona glomerulosa) and lipidosis (zona fasciculata) of the adrenals, glomerulonephrosis (associated with changes in blood urea nitrogen, total protein, and albumin levels), hepatocellular hypertrophy and increased heart weight.

The main adverse effects of the combination noted in the current 2 week dose range finding study occurred primarily in the cecum and colon at doses of 100/3 and 300/10 mg/kg/day and included local inflammatory responses and hypertrophy/hyperplasia, consistent with previous findings for aliskiren alone.

In the 13 week rat study, the adverse effects of the combination were mainly noted in the high dose (HD) combination group (300/10 mg/kg/day) or monotherapy groups, with most of the findings showing reversal after the 4 week recovery period:

- Premature deaths and clinical signs of shallow/deep laboured breathing, abnormal breathing sounds and salivation were seen with the HD combination or 300 mg/kg/day of aliskiren alone. The findings were consistent with those observed in a previous 13 week rat study with aliskiren and are attributable to a local irritation effect of aliskiren as a result of aspiration of the dosing solution into the respiratory tract.
- Clinical pathology parameters were minimally affected, with slight decreases in mean lymphocyte counts and decreases in globulin concentrations observed in the HD combination group and the amlodipine group.
- Pathological findings included pale discoloration or foci of the adrenals and corresponding histopathological changes of minimal hypertrophy/vacuolation of the zona glomerulosa in rats given amlodipine alone or the HD combination. Adrenals findings were consistent with those previously observed for amlodipine monotherapy and were not noted in the current aliskiren monotherapy group. Moreover, the number of the animals with adrenal findings was higher in the amlodipine treated group than in the combination groups.

No novel treatment related toxicities or potentiation of known toxicities were identified with the aliskiren/amlodipine combination in animal studies, consistent with the absence of novel adverse reactions in the clinical trial data.

Impurity qualification

Aliskiren related impurities

Using the TGA-adopted EU guideline, the qualification threshold for aliskiren related degradation products (maximum daily dose of aliskiren is 300 mg) is 0.2%.[9] The proposed shelf life limits for four aliskiren related impurities exceed this threshold.

The sponsor was asked to justify the specifications for the aliskiren related impurities. The sponsor noted that potential general and genetic toxicities of these impurities have been evaluated in previously submitted applications and that based on these data, the four impurities were considered toxicologically qualified for the proposed specifications.

This response was considered acceptable.

Amlodipine related impurities

Using the TGA-adopted EU guideline, the qualification threshold for amlodipine related degradation products (maximum daily dose of amlodipine is 10 mg) is not more than (NMT) 0.5%. One impurity exceeds this threshold. Therefore, this impurity was added to the combination test item used in the repeat dose and genotoxicity studies in order to qualify it at the specified expiry limit of 1.7% (based on amlodipine).

No novel toxicities attributable to the administration of the impurity were observed in the 13 week repeat dose toxicity study in rats at a relative exposure of 8.9 based on $mg/m^2/day$.

Genotoxicity testing of the impurity was conducted in the presence of the active pharmaceutical ingredient in an Ames test and an *in vitro* test with cytogenetic evaluation of chromosomal damage in mammalian cells. No *in vivo* test for chromosomal damage in rodent hematopoietic cells was performed.

At the 0.05% level of the impurity used in the negative Ames test the actual concentrations of the impurity tested were 15.1, 30.2, 60.5, 121 and 241.9 µg/plate. Given the potential experimental interference which may occur when testing impurities in the presence of the active pharmaceutical ingredient, it may have been preferable to test the impurity neat at concentrations of ≥ 250 µg/plate in this bacterial mutagenicity assay (Müller *et al.*, 2006; Kenyon *et al*., 2007).[10,11]

Under the conditions used in a chromosome aberration test with cultured human peripheral blood lymphocytes, the test article did not show clastogenic potential.

Overall, the available nonclinical safety data from repeat dose and genotoxicity studies was sufficient to qualify all of the nominated impurities at the proposed specifications.

Pregnancy categorisation

The sponsor proposed Pregnancy Category D, which is dictated by the ability of aliskiren to block the RAAS. Previous clinical experience has shown that drugs with this activity can cause fetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters.

[9] EMEA, ICH Topic Q 3 B (R2), June 2006. Note for Guidance on Impurities in New Drug Products, CPMP/ICH/2738/99.

[10] Müller L, Mauthe RJ, Riley CM et al. A rationale for determining, testing, and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity. Regulatory Toxicology and Pharmacology 2006; 44: 198–211.

[11] Kenyon MO, Cheung JR, Dobo KL, Ku WW. An evaluation of the sensitivity of the Ames assay to discern low-level mutagenic impurities. Regulatory Toxicology and Pharmacology 2007; 48: 75-86.

Nonclinical Summary and Conclusions

The sponsor submitted a suitable bridging data package consisting of 2 week and 13 week PO repeat dose toxicity studies in rats (including toxicokinetics) plus *in vitro* tests of mutagenicity and chromosomal aberration to qualify impurities. All pivotal studies were GLP compliant.

The submitted nonclinical bridging data for the aliskiren/amlodipine fixed combination did not address efficacy or pharmacodynamic interactions. This will rely on clinical trial data.

The test item in all studies was a special batch of aliskiren/amlodipine combined at the clinically intended ratio (30:1) that contained additional amounts of an amlodipine related degradation product in order to qualify this impurity at the proposed expiry limit of 1.7% (based on amlodipine content).

The absence of nonclinical PD studies with the combination was justified by the sponsor on the basis of a lack of appropriate animal PD models as well as consideration of the large amount of experimental and clinical data showing greater blood pressure reductions (than monotherapy) of combinations of calcium channel blockers (CCB) and RAAS blockers such as ACE inhibitors or ARBs.

Toxicokinetic data from the 13 week combination toxicity study in rats failed to reveal any significant pharmacokinetic interactions between aliskiren and amlodipine, consistent with their different individual routes of metabolism and elimination (aliskiren: primary elimination into bile via MDR1; amlodipine: extensive hepatic metabolism by CYP3A).

Relative exposure (based on AUC) attained in the 13 week repeat dose combination study in rats was less than or equal to 1 for aliskiren, and ranged from 0.3 to 8.5 for amlodipine. Nevertheless, systemic exposure to these drugs was sufficiently high in all studies to elicit microscopic tissue findings.

Toxicities observed with the combination included clinical signs of respiratory system distress and microscopic findings in the gastrointestinal tract (aliskiren) and microscopic findings in the adrenals associated with amlodipine. Overall, the toxicological profile of the combination was consistent with those previously established for aliskiren and amlodipine when used as monotherapy. No new toxicities or potentiated known toxicities were noted with the combination. The amlodipine related degradant was negative when tested with the API in *in vitro* assays for bacterial reverse mutation and mammalian chromosomal damage. This data, plus previously submitted toxicology data were sufficient to qualify all of the nominated impurities at the proposed shelf life specifications.

There were no nonclinical objections to the registration of Rasilamlo for the treatment of hypertension.

IV. Clinical Findings

Introduction

The clinical program included 5570 mild to moderate hypertensive patients and 2835 of whom receive at least one dose of aliskiren/amlodipine combination and 612 received the combination for at least 6 months. There were seven main clinical studies: one short term placebo controlled; three short term active controlled; one long term controlled and its extension study; and one long term uncontrolled.

Pharmacokinetics

Introduction

Aliskiren belongs to a class of anti-hypertensives called direct renin inhibitors (DRI) that act by directly inhibiting the RAAS at the initial rate-limiting step, the conversion of angiotensinogen to angiotensin I (Ang I). Amlodipine is a long acting, dihydropyridine CCB.

The PK section of this evaluation comprised 4 open label, randomised bioavailability and bioequivalence studies, which examined 336 healthy subjects (8 female), aged 18 to 45 years.

Methods

The pharmacokinetics and pharmacodynamics of aliskiren and amlodipine have been previously determined and both exhibit linear pharmacokinetics within their respective clinical dose range. In general, descriptive statistics of PK parameters including mean, standard deviation (SD), and coefficient of variation, minimum and maximum values were determined using non-compartmental methods in WinNonlin Pro. Median values and ranges were given for T_{max}.

Absorption

Bioavailability

Study SPA100A22101 was an open label, randomised, five treatment, single dose, five period crossover study conducted in 60 healthy subjects (8 female), aged 19 to 45 years, to determine the relative bioavailability of the fixed dose combination of 300/10 mg aliskiren/amlodipine market formulation tablet variants and the free combination of the market formulation of 300 mg aliskiren tablet and the market formulation of 2 x 5 mg amlodipine tablets. This study was summarised in *Section II*.

The relative bioavailability of aliskiren and amlodipine from the fixed combination tablet variants versus the free combination market tablets was assessed in order to select a formulation for further clinical development. C_{max} for the five treatments ranged from 230 to 265 ng/mL and the area under the plasma concentration time curve from time zero to infinity (AUC_{inf}) ranged from 1856 to 2069 h.ng/mL. The results of the statistical analysis indicate that one variant 004 was bioequivalent (90% CI of the geometric mean ratio contained within 80-125%) in regards to both AUC and C_{max} of aliskiren compared to the free combination. Although the three other variants met bioequivalence standards for AUC they failed for C_{max} (lower bound of 90% CI slightly below 80%) of aliskiren. For amlodipine, all test variants were bioequivalent to the free combination for both AUC and C_{max}. Based on these results, that variant was selected for further clinical development.

Bioequivalence

Study SPA100A22102 was an open label, randomised, two treatment, two period, single dose, crossover study which examined the bioequivalence of a fixed combination of SPA100 (aliskiren/amlodipine 300/10 mg oral tablet) and the free combination of aliskiren 300 mg market tablet and amlodipine 10 mg over-encapsulated market tablets (2 x 5 mg) in 120 healthy male subjects, aged 18 to 45 years. This study was summarised in *Section II*.

For aliskiren the C_{max} (fixed vs free = 361 vs 369 ng/mL), the area under the plasma concentration time to the last measurable time (AUC_{last}) (2380 vs 2495 ng.h/mL) and AUC_{inf} (2528 vs 2651 ng.h/mL) were bioequivalent for both drug regimens. Similarly, for

amlodipine, the C_{max} (fixed vs free = 4.87 vs 4.97 ng/mL), AUC_{last} (283 vs 290 ng.h/mL) and AUC_{inf} (314 vs 324 ng.h/mL) were also bioequivalent for the two regimens.

SPA100A22103 was an open label, randomised, two treatment, two period, single dose, crossover study which examined the bioequivalence of a fixed combination of SPA100 (aliskiren/amlodipine 150/10 mg oral tablet) and the free combination of aliskiren 150 mg market tablet and amlodipine 10 mg over-encapsulated market tablets (2 x 5 mg) in 120 healthy male subjects, aged 18 to 41 years. This study was summarised in *Section II*.

For aliskiren, the C_{max} (fixed vs free = 209 vs 221 ng/mL), AUC_{last} (1354 vs 1431 ng.h/mL) and AUC_{inf} (1479 vs 1532 ng.h/mL) were bioequivalent for both drug regimens. Similarly, for amlodipine, the C_{max} (fixed vs free = 5.48 vs 5.56 ng/mL), AUC_{last} (313 vs 318 ng.h/mL) and AUC_{inf} (360 vs 366 ng.h/mL) were also bioequivalent for the two regimens.

Influence of food

Study SPA100A22104 was a single centre, open label, randomised, two period, crossover, single dose study which examined the effect of food on the bioavailability of fixed combination SPA100 (aliskiren/amlodipine 300/10 mg oral tablets) in 36 healthy males, aged 20 to 43 years. This study was summarised in *Section II*.

Aliskiren plasma concentrations increased quickly with a median T_{max} of 1.5 hours (h) (ranging from 1.0 h to 6.0 h) under fasted conditions. Food delayed the absorption of aliskiren with a median T_{max} observed to be 3.0 h (ranging from 1.0 h to 10.0 h). Food reduced the C_{max} and AUC_{inf} of aliskiren by approximately 90% (arithmetic mean from 311 ng/mL to 26.7 ng/mL) and approximately 80% (AUC_{inf} from 2347 ng.h/mL to 480 ng.h/mL), respectively, compared to fasted conditions. However, there was no significant difference in the elimination half-life ($t_{1/2}$) of aliskiren between the fed and fasted subjects (49.0 h vs 57.9 h, respectively). Amlodipine, by contrast was absorbed more slowly with a median T_{max} of 8 h and the absorption was similar under fed and fasted conditions. Both the mean C_{max} (4.93 vs 4.87 ng/mL) and AUC_{inf} (337 vs 333 ng.h/mL) of amlodipine were similar under fed and fasted conditions. The elimination half-lives of amlodipine ($t_{1/2}$) were also similar (49.6 h vs 50.1 h) when the fixed dose combination of aliskiren/amlodipine 300/10 mg was administered under fed or fasted conditions. As food significantly affects the PKs of aliskiren, the combination tablet should only be taken under fasted conditions.

Evaluator's overall conclusions on pharmacokinetics

One variant was bioequivalent with the free combination of these drugs.

A high fat meal increased the median T_{max} of aliskiren from 1.5 h to 3.0 h. In addition, food reduced the C_{max} and AUC_{inf} of aliskiren by approximately 90% and 80%, respectively compared to fasted conditions. By contrast, food had little effect on the T_{max}, C_{max} and AUC_{inf} of amlodipine.

The sponsor only demonstrated the bioequivalence of the 300/10 mg and the 150/10 mg doses of the fixed combination tablets with the corresponding doses of the individual drug. No information was provided regarding the bioequivalence of the other proposed dosage strengths (150/5 mg and 300/5 mg) that are contained in the application (but see *Section II*).

Pharmacodynamics

The pharmacodynamics of the individual drugs, aliskiren and amlodipine, used in this combination are already well established. No new data were submitted in this application for the combination drug.

Efficacy

Introduction

The submission contained four short term studies: one placebo controlled (SPA2305) and three active controlled (SPA2303, SPA2304 and SPP2305). There were also two long term studies: one active controlled (SPP2323 and its extension study SPP2323E1) and one open label (SPA2301) (Table 6). The long term, controlled study was not of the aliskiren/amlodipine combination but of aliskiren monotherapy compared to hydrochlorothiazide (HCT) with optional add-on amlodipine. In addition, one short term active controlled study used aliskiren plus amlodipine (SPP2305) rather than the proposed combination tablet. The primary efficacy measure was change from baseline in the mean sitting diastolic blood pressure (msDBP); mean sitting systolic BP (msSBP) and BP response rates were secondary endpoints. Efficacy data were not pooled due to the different study designs. The dose selection was based on the commonly used doses of the individual medications.

Table 6: List of Clinical efficacy and safety studies pertinent to the claimed indication

Topic Purpose	Source of data Free or fixed combination
Dose selection	**None:** The dose selection for aliskiren/amlodipine fixed combination products (SPA100) was based on approved doses of the respective monotherapy, and confirmed in the placebo-controlled multifactorial Study SPA2305 and non-responder Studies SPA2303 and SPA2304.
Short-term, placebo-controlled study Pivotal placebo-controlled study including data supporting initial therapy use of aliskiren/amlodipine combination	**Study SPA2305:** double-blind, placebo-controlled 3 x 3 multifactorial study with aliskiren monotherapy, amlodipine monotherapy, and aliskiren/amlodipine combination, with a 24-hour ABPM substudy. **Fixed combination**
Short-term, active-controlled studies	
Study supporting the use of aliskiren/amlodipine combination in patients not adequately responding to aliskiren monotherapy	**Study SPA2303:** double-blind, active-controlled study evaluating the combination of aliskiren/amlodipine (300/5 mg) and aliskiren/amlodipine (300/10 mg) compared to aliskiren 300 mg in non-responders to aliskiren 300 mg. **Fixed combination**
Studies supporting the use of aliskiren/amlodipine combination in patients not responding to amlodipine monotherapy	**Study SPA2304:** double-blind, active-controlled study evaluating the combination of aliskiren/amlodipine (150/10 mg) and aliskiren/amlodipine (300/10 mg) compared to amlodipine 10 mg in non-responders to amlodipine 10 mg. **Fixed combination**
	Study SPP2305: double-blind, active-controlled study evaluating the combination of aliskiren/amlodipine (150/5 mg) compared to amlodipine 5 mg and amlodipine 10 mg in non-responders to amlodipine 5 mg. **Free combination**
Long-term uncontrolled study Uncontrolled, supportive study supporting the long-term use of the aliskiren/amlodipine combination	**Study SPA2301:** open-label 54-week study evaluating the long-term safety and efficacy of aliskiren/amlodipine 300/10 mg with optional addition of HCTZ. **Free combination**
Long-term controlled studies Controlled, supportive studies supporting the long-term use of the aliskiren/amlodipine combination	**Study SPP2323*:** double-blind 26-week study, evaluating aliskiren monotherapy (300 mg) vs. HCTZ (25 mg) with optional addition of amlodipine. **Study SPP2323E1*:** a 26-week extension to Study SPP2323. Patients continued on same treatment from double-blind study. **Free combination**

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

Dose Response Studies

There were no dose response studies included in the submission. The proposed dosage in the combination tablets is the same as the doses used in the respective monotherapies for hypertension treatment, that is, 150 mg and 300 mg for aliskiren and 5 mg and 10 mg for amlodipine.

Main (pivotal) Studies

SPA2305 (short term placebo controlled)

Methods

Study number SPA100A2305 (SPA2305) was an 8 week double blind, multicentre, randomized, multifactorial, placebo controlled, parallel group study to evaluate the efficacy and safety of aliskiren administered alone and in combination with amlodipine in 1688 patients with essential hypertension. There were 3 study periods: Period 1 was a 3 day washout; Period 2 was a single blind placebo run-in period of 2 to 4 weeks duration to establish baseline BP and eligibility; and Period 3 was an 8 week randomised, double blind treatment period. Subjects were randomised to one of 9 treatment groups: aliskiren 150 mg; aliskiren 300 mg; amlodipine 5 mg; amlodipine 10 mg; the combination of aliskiren/amlodipine 150/5 mg; 150/10 mg; 300/5 mg; 300/10 mg; or placebo. Those randomised to 10 mg amlodipine started on 5 mg and had a forced titration after 1 week.

Blood pressure measurements were made with an automated BP monitor. Sitting and standing BP was measured at trough (24 h ±3 h). Ambulatory BP monitoring (ABPM) was performed in a subset of patients over two 24 h periods at the start and end of double blind treatment.

Objectives

The primary objective was to demonstrate that the efficacy of the fixed dose combination of aliskiren/amlodipine was superior to both monotherapies in patients with essential hypertension as measured by a reduction in msDBP from baseline to end of study. Secondary objectives included: assessment of msSBP change from baseline; response rates on blood pressure control (msSBP <140 mmHg and msDBP <90 mmHg); response rates on DBP (msDBP <90 mmHg or a reduction ≥10 mmHg from baseline) and SBP (msSBP <140 mmHg or a reduction ≥20 mmHg from baseline); 24 h BP profile on 24 h ABPM; and safety including effect on amlodipine-induced oedema. A subset of patients was also assessed for the effect on plasma renin concentration (PRC) and plasma renin activity (PRA).

Study participants

Inclusion criteria were: ≥18 years of age; msDBP ≥ 90 mmHg and < 110 mmHg at the visit prior to the randomisation visit; msDBP ≥ 95 mmHg and < 110 mmHg at the randomisation visit; and an absolute difference of ≤ 10 mmHg in the msDBP during the last 2 visits of the single blind run-in period.

Exclusion criteria were: previous treatment with aliskiren/amlodipine combination in a clinical trial; severe hypertension (msDBP ≥110 mmHg and/or msSBP ≥180 mmHg); pregnancy or lactation; women of child bearing potential unless using 2 methods of birth control; secondary hypertension; Grade III or IV hypertensive retinopathy; hypertensive encephalopathy, cerebrovascular accident, transient ischaemic attach (TIA), myocardial infarction (MI), coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI); heart failure (New York Heart Association [NYHA] Class II-IV); serum potassium ≥ 5.3 mEq/L (mmol/L); type I or II diabetes mellitus which was not well controlled; angina pectoris requiring medication (except nitrates); second or third degree heart block without pacemaker or life threatening arrhythmia in last 12 months;

symptomatic valvular heart disease; major gastrointestinal surgery with bowel resection; active inflammatory bowel disease within 12 months; active gastritis, ulcers or bleeding within 3 months; hepatic disease including alanine transaminase (ALT) or aspartate transaminase (AST) > 3x the upper limit of normal (ULN), history of hepatic encephalopathy, oesophageal varices or portocaval shunt; renal impairment with glomerular filtration rate (GFR) <30 mL/min or dialysis or history of nephrotic syndrome; known or suspected contraindications to CCB or renin inhibitors; malignancy within the past 5 years; drug and alcohol abuse within 12 months; likely to need a forbidden medication; and for the ABPM substudy an upper arm circumference >42 cm and shift workers.

The study drug was discontinued if msDBP ≥110 mmHg or msSBP ≥180 mmHg or if clinically significant hypotension and/or msDBP <60 mmHg and/or msSBP <100 mmHg at any time during the study.

Outcomes/endpoints

The primary efficacy variable was the change from baseline to the end of the study in the mean sitting diastolic blood pressure (msDBP). The BP was defined as the average of the available readings from one visit. Secondary variables included the change from baseline in msSBP as well as percent of patients responding and changes from baseline in ABPM. The hourly mean ambulatory DBP (MADBP) and SBP (MASBP) was the average of readings taken in the corresponding hour.

The primary analysis population was the "full analysis" set (FAS) which was all randomised patients excluding those misrandomised (that is, did not qualify but were inadvertently randomised). Supportive analysis was conducted on the "per protocol" set (PPS) which was all FAS patients who completed the study without any major protocol deviation. The last post baseline BP measurement during double blind treatment was carried forward to analysis (LOCF).

Statistical Considerations

A sample size of 161 completed patients per group had a 90% power to detect a 3.2 mmHg difference in msDBP between combination and monotherapy treatments at a 2-sided significance level of 0.05, assuming a SD of 8 mmHg. Assuming a dropout rate of 10%, 179 patients per arm, and 1611 in total, were required. This sample also had 90% power for the Hung's AVE test (Hung 2000).[12] For the ABPM substudy, 1026 patients were required (1143 to allow for drop out), or 114 completed per group, to give the study an 80% power to detect a difference of 3.0 mmHg between the combination and monotherapy treatment (α=0.05). Patients were randomised in a 1:1:1:1:1:1:1:1:1 ratio to one of the 9 treatment arms by an interactive voice response system (IVRS).

To assess whether both monotherapy treatments (aliskiren and amlodipine) contributed to the overall effect in BP reduction of the combination treatment, the primary variable at endpoint was analysed by Hung's AVE test (Hung 2000).[12] If the AVE test was statistically significant (in favour of the combination treatment), it was concluded that the aliskiren/amlodipine combination treatment was superior in reducing the msDBP from baseline to endpoint compared to aliskiren and amlodipine monotherapies. Additional analyses included two way analysis of covariance (ANCOVA) with treatment and geographic region as factors and the baseline as a covariate. For a given combination dose, the null hypothesis to be tested was that the combination dose was at most as good as one of its respective monotherapy doses. The proportion of patients responding to each

[12] Hung H. Evaluation of a combination drug with multiple doses in unbalanced factorial design clinical trials. Statistics in Medicine 2000; 19: 2079-2087.

treatment was analysed using a logistic regression model with treatment and region as factors and baseline BP as a covariate. The hourly change from baseline in MADBP or MASBP was analysed by repeated measures ANCOVA.

Results

The study was conducted in 2008-2009 at 208 centres in Eastern and Western Europe, North and South America, Australia and Taiwan.

There were 2694 patients enrolled of whom 1685 completed the single blind placebo run-in period. For the 37.5% who discontinued, the most common reason was abnormal test procedure (30.1%) which included BP criteria. There were 1688 patients randomised, 3 misrandomised who did not receive double blind treatment and 1539 (91.2%) who completed the study. Premature discontinuation (8.6% overall) was highest in the placebo group (15.2%) followed by the amlodipine 10 mg group (10.5%) with the most common reasons being unsatisfactory treatment effect (1.7%) and adverse effects (AEs) (1.7%). Discontinuation due to AEs was greatest in the amlodipine 10 mg group (3.9%) and ranged from 0.5% to 2.2% in the other groups. Protocol deviations that led to exclusion from the PPS occurred in 14.6% of patients with 3.1% of patients taking a forbidden medication that affected BP and 5.6% having msDBP measurements with >10 mmHg difference between visits in the run-in period. The FAS included 1685 (99.8%) subjects and the PPS 1348 (79.9%) subjects.

The various treatment groups were comparable with respect to baseline demographics and disease characteristics. Most subjects were Caucasian (62%) or Black (20%); 17% were aged ≥ 65 years (mean age 54.1 years) and half were male. Forty six percent of subjects were obese (body mass index [BMI] ≥30 kg/m^2), 46.0% had the metabolic syndrome[13] and 11.0% diabetes. The mean duration of hypertension was 7.8 years (excluding the 7.3% of patients who were treatment naïve). Baseline BP measurements were also comparable across treatment groups with a msDBP of 99.4 to 100.1 and msSBP of 156.5 to 158.9 mmHg. The most frequently reported medical conditions were hypercholesterolaemia (8.5%), dyslipidaemia (8.2%), obesity (7.6%) and osteoarthritis (7.3%). Prior antihypertensive medications included: ACE inhibitors (24.3% overall), CCB (17.6% including amlodipine 10.6%), ARBs (15.4%), diuretics (14.2%) and beta blockers (10.6%). Prior use of aliskiren was reported for 0.2% of patients. Other common medications included salicylic acid (12.9%), HMG CoA reductase inhibitors (10.8%), anilides (7.2%) and topical NSAIDs (10.8%).

Primary outcome

There was a statistically significant ($p<0.001$) greater reduction in the msDBP of at least one aliskiren/amlodipine combination compared to both monotherapy groups (Hung's AVE test). The least squares mean difference in change from baseline in msDBP for aliskiren/amlodipine compared to the monotherapies ranged from -2.3 to -8.2 mmHg and all pairwise comparisons were statistically significant. All active treatments had significantly greater msDBP reductions than placebo (Table 7).

[13] Metabolic Syndrome if any 3 of the following 5 are true: 1. Waist circumference> 102 cm (40 in) for men, or > 88 cm (35 in) for women; 2. Triglycerides >= 150 mg/dL (1.69 mmol/L); 3. HDL cholesterol <40 mg/dL (1.04 mmol/L) for men, or <50 mg/dL (1.29 mmol/L) for women; 4. SBP>= 130 or DBP >=85 mmHg; 5. Fasting glucose >= 110 mg/dL (6.1 mmol/L).

Table 7: Study SPA2305 – Statistical analysis of the change from baseline in mean sitting systolic blood pressure at endpoint (FAS)

Treatment Group	N	LSM change from baseline (mmHg) (SE)
Placebo	198	-5.35 (0.62)
Ali 150 mg	193	-7.99 (0.63)
Ali 300 mg	201	-10.19 (0.62)
Aml 5 mg	184	-11.0 (0.65)
Aml 10 mg	179	-13.82 (0.66)
Ali/Aml 150/5 mg	179	-13.98 (0.66)
Ali/Aml 150/10 mg	179	-16.16 (0.66)
Ali/Aml 300/5 mg	175	-14.99 (0.66)
Ali/Aml 300/10 mg	183	-16.45 (0.65)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value
Ali 150 mg vs. Placebo	-2.64 (0.88)	(-4.37, -0.91)	0.003*
Ali 300 mg vs. Placebo	-4.85 (0.87)	(-6.55, -3.14)	<.001*
Aml 5 mg vs. Placebo	-5.66 (0.89)	(-7.40, -3.91)	<.001*
Aml 10 mg vs. Placebo	-8.47 (0.90)	(-10.24, -6.71)	<.001*
Ali/Aml 150/5 mg vs. Ali 150 mg	-6.00 (0.90)	(-7.77, -4.22)	<.001*
Ali/Aml 150/5 mg vs. Aml 5 mg	-2.98 (0.91)	(-4.77, -1.19)	0.001*
Ali/Aml 150/5 mg vs. Placebo	-8.63 (0.90)	(-10.39, -6.87)	<.001*
Ali/Aml 150/10 mg vs. Ali 150 mg	-8.17 (0.90)	(-9.94, -6.40)	<.001*
Ali/Aml 150/10 mg vs. Aml 10 mg	-2.33 (0.92)	(-4.14, -0.53)	0.011*
Ali/Aml 150/10 mg vs. Placebo	-10.81 (0.90)	(-12.57, -9.05)	<.001*
Ali/Aml 300/5 mg vs. Ali 300 mg	-4.79 (0.90)	(-6.56, -3.03)	<.001*
Ali/Aml 300/5 mg vs. Aml 5 mg	-3.98 (0.92)	(-5.78, -2.18)	<.001*
Ali/Aml 300/5 mg vs. Placebo	-9.64 (0.90)	(-11.41, -7.87)	<.001*
Ali/Aml 300/10 mg vs. Ali 300 mg	-6.26 (0.89)	(-8.00, -4.51)	<.001*
Ali/Aml 300/10 mg vs. Aml 10 mg	-2.63 (0.92)	(-4.42, -0.83)	0.004*
Ali/Aml 300/10 mg vs. Placebo	-11.10 (0.89)	(-12.85, -9.35)	<.001*

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

Only patients with both baseline and post-baseline values are included.

Least square 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

Secondary Outcomes

For msSBP there was a statistically significant (p<0.001) greater reduction of at least one aliskiren/amlodipine combination compared to both monotherapy groups (Hung's AVE test). The aliskiren/amlodipine combinations with 10 mg amlodipine did not had a significantly greater reduction in msSBP than amlodipine 10 mg alone: aliskiren/amlodipine 150/10 mg vs amlodipine 10 mg least square mean (LSM) difference in change from baseline of -2.83 mmHg, p=0.056; aliskiren/amlodipine 300/10 mg vs amlodipine 10 mg LSM difference -2.16 mmHg, p=0.143. There was a statistically significant greater reduction in msSBP in all other pairwise comparisons and all active treatment groups had significantly greater reduction in msSBP than placebo. Placebo subtracted mean reductions in msDBP and msSBP are shown in Table 8.

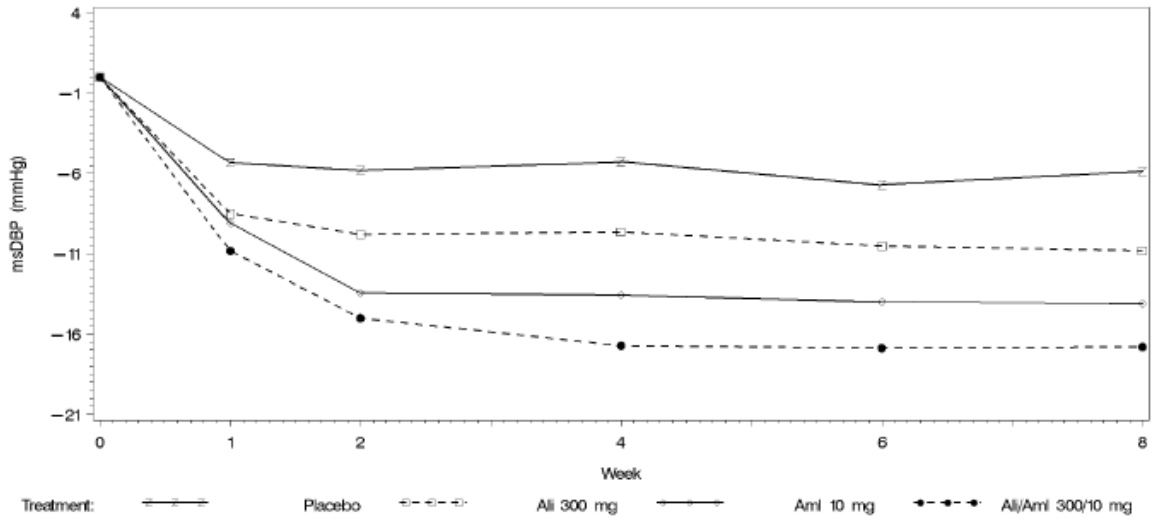
Table 8: Study SPA2305 – Placebo subtracted LS mean reduction in msDBP and msSBP at endpoint (FAS)

	Change in msDBP (mmHg) (primary efficacy variable)		
	Placebo	**Aliskiren 150 mg**	**Aliskiren 300 mg**
Placebo	---	-2.64 [a]	-4.85 [a]
Amlodipine 5 mg	-5.66 [a]	-8.63 [a, b, c]	-9.64 [a, b, c]
Amlodipine 10 mg	-8.47 [a]	-10.81 [a, b, c]	-11.10 [a, b, c]
	Change in msSBP (mmHg) (secondary efficacy variable)		
	Placebo	**Aliskiren 150 mg**	**Aliskiren 300 mg**
Placebo	---	-3.88 [a]	-8.58 [a]
Amlodipine 5 mg	-9.03 [a]	-13.85 [a, b, c]	-15.03 [a, b, c]
Amlodipine 10 mg	-14.25 [a]	-17.08 [a, b]	-16.40 [a, b]

msDBP/msSBP = mean sitting diastolic/systolic blood pressure
Only patients with both baseline and post-baseline values are included.
Placebo's change from baseline of msDBP and msSBP are -5.35 mmHg and -6.79 mmHg, respectively.
[a] statistically significant difference vs. placebo ($p < 0.05$)
[b] statistically significant difference vs. aliskiren component ($p < 0.05$)
[c] statistically significant difference vs. amlodipine component ($p < 0.05$)

For aliskiren/amlodipine 300 mg/10 mg, a reduction in msDBP and msSBP was evident by 1 week, reached maximal effect by 4 weeks, was maintained to 8 weeks and was greater than the respective monotherapies (Figure 2). A similar pattern was seen for other dose combinations.

Figure 2: Study SPA2305 – Change from baseline in msDBP by week for aliskiren/amlodipine 300/10 versus concomitant therapies and placebo (FAS)



BP Control

BP control was defined as msDBP <90 mmHg and msSBP <140 mmHg. All aliskiren/amlodipine combinations had a statistically significant greater rate of BP control than monotherapies at study end. The highest control rate was 68.3% with the highest dose aliskiren/amlodipine 300 mg/10 mg and this was greater than the control rate of 50.3% with amlodipine 10mg.

Response rates

Diastolic BP response (msDBP <90 mmHg or a ≥10 mmHg reduction from baseline) was greatest for aliskiren/amlodipine 300/10 mg at 84.7% and all combinations had significantly greater response rates than monotherapy. For systolic BP response (msSBP <140 mmHg or at least 20 mmHg reduction from baseline) the greatest response was again with aliskiren/amlodipine 300/10 mg (80.3%). Aliskiren/amlodipine 150 mg/10 mg and 300 mg/10 mg did not have a significantly greater response rate on SBP than amlodipine 10 mg (p=0.28 and p=0.06 respectively), though other combinations did have a significantly greater response rate than the respective monotherapies.

Per protocol analysis (79.9% of patients) was consistent with the FAS results for change from baseline in msDBP, msSBP, BP control rate and responder rates.

Ambulatory BP

For a subset of 819 patients (352 treated with aliskiren/amlodipine), the mean 24 hour ambulatory DBP and SBP was significantly (p<0.001) reduced in all combinations of aliskiren/amlodipine compared to the monotherapies with differences of 4.68 to 10.72 mmHg for SBP and 3.56 to 6.67 mmHg for DBP. There was little placebo effect noted on mean 24 h ambulatory BP, with a change from baseline of 0.73 mmHg for DBP and -0.01 mmHg for SBP. Placebo subtracted mean reduction in MADBP and MASBP are presented in Table 9.

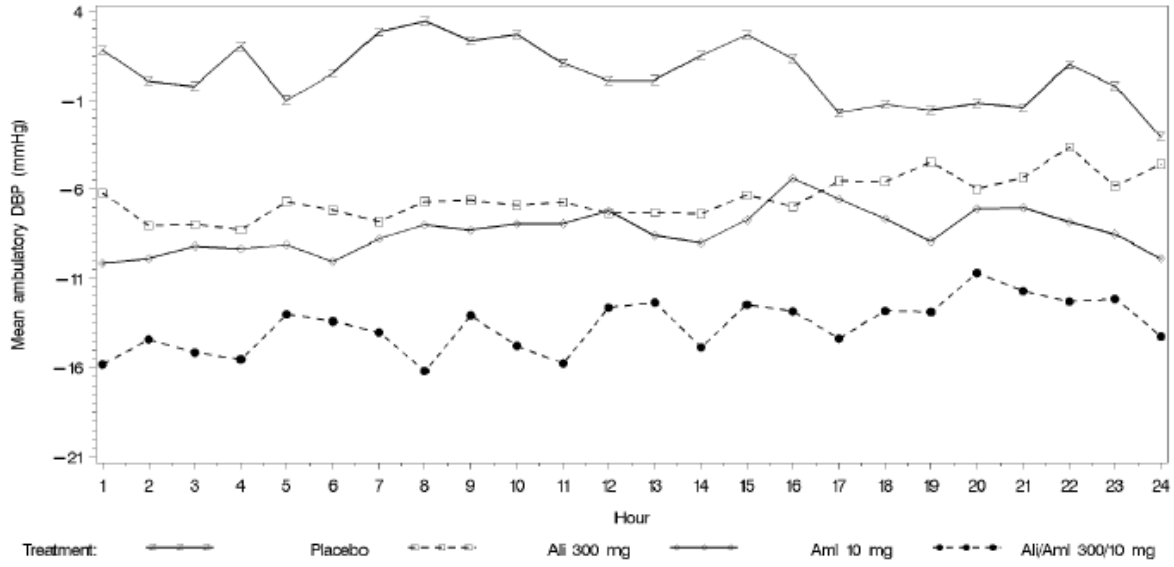
Table 9: Study SPA2305 – Placebo subtracted LS mean reduction in mean 24 hour MADBP and MASBP at endpoint (FAS)

Change in MADBP (mmHg)			
	Placebo	Aliskiren 150 mg	Aliskiren 300 mg
Placebo	---	-5.02 [a]	-7.04 [a]
Amlodipine 5 mg	-5.69 [a]	-9.59 [a, b, c]	-10.77 [a, b, c]
Amlodipine 10 mg	-8.62 [a]	-12.18 [a, b, c]	-13.71 [a, b, c]
Change in MASBP (mmHg)			
	Placebo	Aliskiren 150 mg	Aliskiren 300 mg
Placebo	---	-6.64 [a]	-9.08 [a]
Amlodipine 5 mg	-8.85 [a]	-14.23 [a, b, c]	-15.96 [a, b, c]
Amlodipine 10 mg	-12.58 [a]	-17.27 [a, b, c]	-19.80 [a, b, c]

Placebo's change from baseline of msDBP and msSBP are 0.73 mmHg and -0.01 mmHg, respectively.
[a] statistically significant difference vs. placebo (p <0.05)
[b] statistically significant difference vs. aliskiren component (p <0.05)
[c] statistically significant difference vs. amlodipine component (p <0.05)

Treatment effect was maintained over 24 h (Figure 3) and trough to peak ratios for the combination therapies placebo subtracted msDBP were 0.36, 0.54, 0.46 and 0.57 for aliskiren/amlodipine 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg combinations, respectively. For SBP, the trough to peak ratios were 0.44, 0.52, 0.54 and 0.61 for 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg combinations, respectively. Ambulatory BP was assessed for patients defined as "dippers" whose baseline mean ambulatory DBP at night (6pm to 6am) was ≥10% below that during the day (6am to 6pm). All aliskiren/amlodipine combinations resulted in a greater reduction in ambulatory DBP and SBP compared to monotherapies regardless of "dipper" status.

Figure 3: Study SPA2305 – Change from baseline in MADBP at endpoint by postdosing hour for aliskiren/amlodipine 300/10 versus concomitant therapies and placebo (FAS)



Subgroup analysis

For Caucasians, all combination therapies resulted in a greater reduction in DBP and SBP than the monotherapies. For Black patients (n=336), the numbers in each group were too small to draw meaningful conclusions. For both males and females and those aged <65 years and ≥65 years, the combination therapies resulted in a greater reduction in msDBP and msSBP than the monotherapies. *Post hoc* subgroup analyses reported in the sponsor's *Clinical Summary* found a generally higher BP control rate with the combination therapies than the monotherapies in patients with diabetes, mild to moderately impaired renal function and Stage 2 hypertension (≥ 160/100 mmHg).

Dose response

There was an evident dose response on DBP and SBP.

Biomarkers

About one third of subjects had plasma renin concentration (PRC) and plasma renin activity (PRA) measured. At study end the PRC had increased in all active treatment groups and was highest in the combination groups (249-574% geometric mean change). PRA decreased in groups with aliskiren (55-68%) and increased in amlodipine monotherapy groups (59-73%).

Summary

After 8 weeks of treatment in 1688 patients with essential hypertension, the combination of aliskiren/amlodipine at doses of 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg resulted in statistically significant and clinically meaningful reductions in msDBP compared to the respective monotherapies (differences of -2.3 to -8.2 mmHg). Reduction in msSBP was also seen with the 150/5 mg and 300/5 mg doses, while combinations with 10 mg amlodipine did not produce a greater reduction than amlodipine 10 mg alone. BP control (<140/90 mmHg) was significantly greater with the combinations than the monotherapies with greatest control (68.3%) seen with aliskiren/amlodipine 300 mg/10 mg (compared to 50.3% with amlodipine 10mg). The effect on BP reduction was seen at one week and was maximal at 4 weeks. There was also a significant reduction in mean 24

h ambulatory DBP and SBP and this effect was maintained over the 24 h period with once daily dosing. The combination therapies were effective across subgroups of gender and age, though there were too few blacks to draw conclusions on this racial group.

SPA2303 (short term aliskiren controlled)

Methods

Study SPA2303 was an 8 week randomised, double blind, parallel group study to evaluate the efficacy and safety of the combination of aliskiren/amlodipine (300/5 mg and 300/10 mg) in comparison with aliskiren 300 mg in patients with essential hypertension not adequately responsive to aliskiren 300 mg monotherapy.

After a one week washout, there was a 4 week single blind run-in period on aliskiren 300 mg daily. Patients who did not adequately respond to aliskiren monotherapy (and meeting inclusion/exclusion criteria) were then randomised to an 8 week, double blind treatment period and received 1 of 3 treatments: aliskiren/amlodipine 300/5 mg, aliskiren/amlodipine 300/10 mg or aliskiren 300 mg.

Objectives

The primary objective was to demonstrate efficacy of the combination therapies in hypertensive patients who did not show sufficient BP response to a 4 week treatment of aliskiren 300 mg, with efficacy being a superior reduction in msDBP from baseline to end of study when compared to aliskiren 300 mg. Secondary objectives included effect on msSBP, BP control rate, msDBP and msSBP response rates and safety.

Study participants

Inclusion criteria were: 18 years of age; diagnosis of hypertension with (at the start of the single blind period) a msDBP ≥95 mmHg and <110 mmHg for newly diagnosed and msDBP ≥90 mmHg and <110 mmHg for those previously treated; and msDBP ≥90 mmHg and <110 mmHg at randomisation. Exclusion criteria were the same as SPA2305.

Outcomes/endpoints

The primary efficacy variable was the change from baseline to end of study in msDBP. The analysis population was the FAS with LOCF.

Statistical Considerations

For the study to have 90% power to detect a 2.5 mmHg treatment difference between aliskiren/amlodipine and aliskiren (assuming a standard deviation of 8 mmHg and a 2 sided significance level of 0.05) a sample of 217 per arm, or 651 completed patients, was required. To allow for drop outs, 242 per arm (726 in total) needed to be randomised. Allowing a 60% screen failure rate (including aliskiren 300mg responders), 1815 patients were required to be screened. A sample size of 217 evaluable patients per arm also gave the study a 90% power to detect a sitting SBP difference of 4.37 mmHg, assuming a SD of 14 mmHg. Patients were randomised in a 1:1:1 ratio using an IVRS.

The primary efficacy analysis was a 2 way ANCOVA with treatment and geographic region as factors and baseline as a covariate. Hierarchical multiple testing was undertaken with aliskiren/amlodipine 300/10 mg compared to aliskiren 300 mg and if this was superior then aliskiren/amlodipine 300/5 mg was compared to aliskiren 300 mg. The significance level for the tests was 0.05. BP control and response rates were analysed by logistic regression models.

Results

The study was conducted in 2008-2009 at 97 centres in Estonia, France, Iceland, India, Italy, South Korea, Lithuania, Spain and Venezuela.

There were 1086 subjects enrolled and 820 randomised, with 283, 277 and 260 patients in the aliskiren/amlodipine 300/10 mg, 300/5 mg and aliskiren 300 mg groups, respectively. For the 268 patients who discontinued at the single blind run-in period, 2 were randomised in error and did not receive double blind treatment, 17.6% had abnormal procedure results including not meeting the BP criteria, 2.3% withdrew consent and 2.1% had AEs. There were 777/820 (94.8%) patients who completed the study and 41 (5.0%) who prematurely discontinued, the most common reason being AEs (1.8%) and unsatisfactory therapeutic effect (1.1%). AEs leading to discontinuation were more common in the aliskiren/amlodipine 300/10 mg group (3.5%) compared to aliskiren/amlodipine 300/5 mg (0.4%) or aliskiren 300 mg (1.2%). All 9 patients who withdrew due to unsatisfactory treatment effect were in the aliskiren 300 mg group (3.5%).

Baseline characteristics and medical history were comparable between treatment groups. The study population was 60.5% male, 66.3% Caucasian, 27.0% Asian, with 19.1% aged ≥65 years, 37.8% obese (BMI ≥30 kg/m^2), 46.2% with metabolic syndrome, 9% diabetic and the mean duration of hypertension was 7.8 years. Only 1.6% of patients were treatment naïve. Baseline BP was comparable between groups, msDBP ranged from 96.2 to 96.5 mmHg and msSBP ranged from 150.8 to 151.9 mmHg.

Primary outcome

The change from baseline in the LSM msDBP was -13.07, -10.54 and -5.84 mmHg for aliskiren/amlodipine 300/10 mg, aliskiren/amlodipine 300/5 mg and aliskiren 300 mg groups, respectively. Both aliskiren/amlodipine combinations resulted in a statistically significant (p<0.0001) greater reduction in msDBP over the 8 week treatment period (FAS with LOCF) compared to aliskiren 300 mg (-7.23 mmHg for 300/10 mg and -4.71 mmHg for 300/5 mg) (Table 10). In addition, aliskiren/amlodipine 300/10 mg resulted in a greater effect (-2.5mmHg) than the aliskiren/amlodipine 300/5 mg dose.

Table 10: Study SPA2303 – Statistical analysis of change from baseline in msDBP at endpoint (FAS)

Treatment Group	N	LSM change from baseline (SE)	
Aliskiren/amlodipine 300/10 mg	281	-13.07 (0.463)	
Aliskiren/amlodipine 300/5 mg	274	-10.54 (0.467)	
Aliskiren 300mg	260	-5.84 (0.480)	
Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Aliskiren/amlodipine 300/10 mg vs aliskiren 300 mg	-7.23 (0.638)	(-8.49, -5.98)	<.0001*
Aliskiren/amlodipine 300/5mg vs aliskiren 300 mg	-4.71 (0.642)	(-5.97, -3.45)	<.0001*

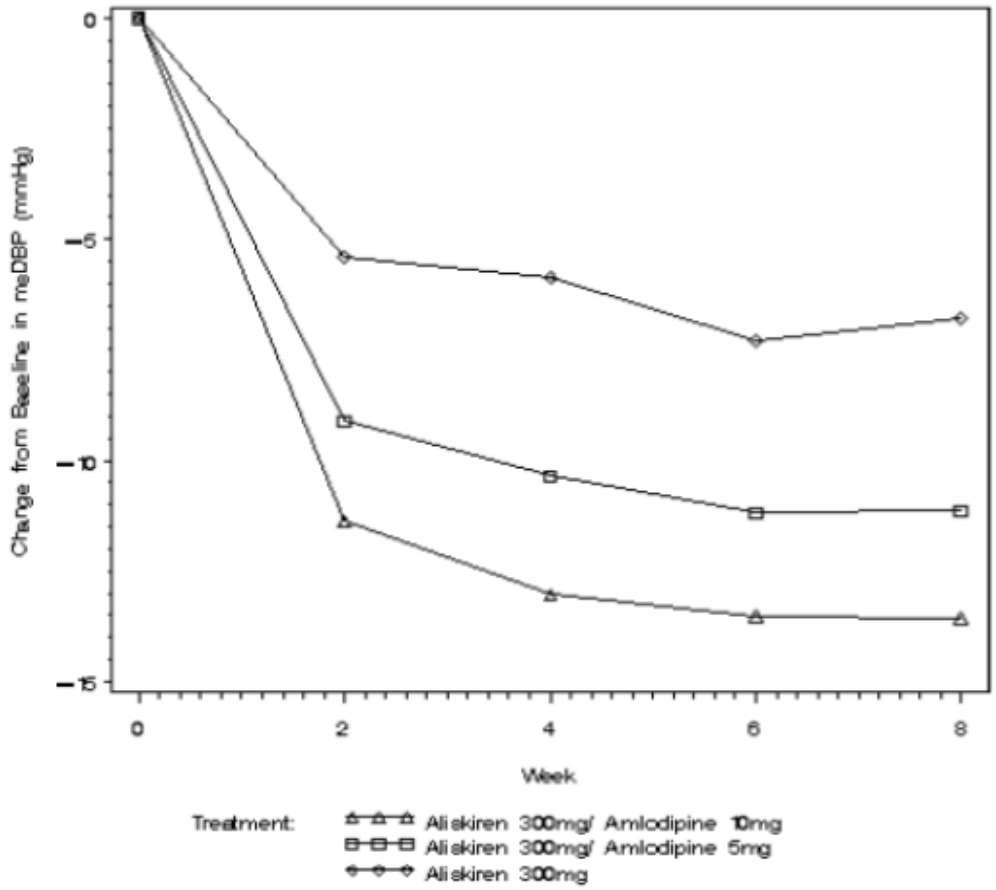
SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval.
Least square means, confidence intervals and p-values were from an ANCOVA model containing treatment, region and baseline msDBP.
* Indicates statistical significance at 0.05 level.
N counts patients who had both baseline and post-baseline measurements. Three patients (1 in aliskiren/amlodipine 300/10 mg group and 2 in aliskiren/amlodipine 300/5 mg group) were excluded from the analysis due to lack of post-baseline assessment

Secondary Outcomes

A LSM change from baseline in msSBP of -18.04, -14.43 and -6.42 mmHg was found for the aliskiren/amlodipine 300/10 mg, aliskiren/amlodipine 300/5 mg and aliskiren 300 mg groups, respectively. There was also a statistically significant greater reduction in msSBP

in the combination groups compared to aliskiren alone (p<0.0001) (-11.62 mmHg for 300/10 mg and -8.01 mmHg for 300/5 mg). DBP and SBP reduction was seen at 2 weeks and was maintained to Week 8 (Figure 4).

Figure 4: Study SPA2303 – Average of change from baseline in msDBP by treatment group and visit (FAS)



Diastolic BP response (<90 mmHg or ≥10 mmHg reduction from baseline) was significantly greater in the combination treatment groups (p<0.0001), with a response in 83.6%, 77.7% and 51.5% of the aliskiren/amlodipine 300/10 mg, aliskiren/amlodipine 300/5 mg and aliskiren 300 mg groups, respectively. Likewise, response on systolic BP (<140 mmHg or ≥20 mmHg reduction from baseline) was significantly greater in the combination groups: 77.2%, 69.2% and 43.8% of the aliskiren/amlodipine 300/10 mg, aliskiren/amlodipine 300/5 mg and aliskiren 300 mg groups, respectively.

BP control (defined as msDBP <90 mmHg and msSBP <140 mmHg) was also higher with the combination treatment groups (65.5% for 300/10 mg and 56.6% for 300/5 mg) compared to the aliskiren 300mg group (31.5%) (p<0.0001 for both comparisons).

Subgroup analysis found the combination treatment resulted in greater reduction of msDBP and msSBP than aliskiren alone in those aged <65 years and ≥65 years, males and females, and in Caucasians and Asians.

Summary

In hypertensive patients who were inadequately controlled with aliskiren 300 mg monotherapy (msDBP ≥90 mmHg and <110 mmHg), the combination of

aliskiren/amlodipine (300/10 mg and 300/5 mg) resulted in a statistically significant ($p<0.0001$) superior reduction in BP compared to aliskiren 300 mg after 8 weeks of treatment. The difference in the change from baseline in msDBP was -7.23 mmHg and -4.71 mmHg and in msSBP was -11.62 mmHg and -8.01 mmHg for 300/5 mg and 300/10 mg groups, respectively which is a clinically meaningful BP reduction. An incremental increase of the 300/10 mg dose over the 300/5 mg dose was also noted. There was also a significantly greater BP control rate with the combination therapy (65.5% and 56.6% for 300/10 mg and 300/5 mg, respectively) compared to aliskiren alone (31.5%). The greater BP reduction was consistent across subgroups of age, gender and race (Caucasian and Asian).

SPA2304 (short term amlodipine 10 mg controlled)

Methods

Study SPA2304 was an 8 week randomised, double blind, parallel group study to evaluate the efficacy and safety of the combination of aliskiren/amlodipine (150/10 mg and 300/10 mg) in comparison with amlodipine 10 mg in patients with essential hypertension not adequately responsive to amlodipine 10 mg monotherapy.

The study design and methods were the same as SPA2303 with a 1 week washout, 4 week single blind run-in period on amlodipine 10 mg daily and an 8 week double blind treatment period in which nonresponders to amlodipine were randomised to one of 3 groups: aliskiren/amlodipine 150/10 mg, aliskiren/amlodipine 300/10 mg and amlodipine 10 mg.

Objectives

The primary objective was to demonstrate efficacy of the combination therapies in hypertensive patients who did not show sufficient BP response to a 4 week treatment of amlodipine 10 mg with efficacy being a superior reduction in msDBP from baseline to end of study when compared to amlodipine 10 mg. Secondary objectives included effect on msSBP, BP control rate, msDBP and msSBP response rates and safety.

Study participants

Inclusion and exclusion criteria were the same as SPA2303.

Outcomes/endpoints

The primary efficacy variable was the change from baseline to end of study in msDBP. The analysis population was the FAS with LOCF.

Statistical Considerations

The sample size calculation was the same as SPA2303 with 651 completed patients, or 217 per group, required. Patients were randomised in a 1:1:1 ratio using an IVRS.

Methods were the same as SPA2303. Hierarchical multiple testing was undertaken with aliskiren/amlodipine 300/10 mg compared to amlodipine 10 mg and, if this was superior, then aliskiren/amlodipine 150/10 mg was compared to amlodipine 10 mg.

Results

The study was conducted in 2008-2009 at 100 centres in Argentina, Germany, Norway, Sweden, Poland, Slovakia and Turkey.

There were 1358 subjects enrolled and 847 randomised with 279, 285 and 283 in the aliskiren/amlodipine 300/10 mg, 150/10 mg and amlodipine 10 mg groups, respectively. For the patients who discontinued at the single blind run-in period, 4 were randomised in error and did not receive double blind treatment, 28.3% had abnormal procedure results

including not meeting the BP criteria, 5.7% had AEs and 2.3% withdrew consent. There were 782/847 (92.3%) patients who completed the study and 61 (7.2%) who prematurely discontinued. Discontinuation rates were highest in the amlodipine group (9.2%) compared to aliskiren/amlodipine groups (6.5% and 6.0% for 300/10 mg and 150/10 mg doses, respectively). Major protocol deviations occurred in 65/847 (7.7%) patients (8.6%, 6.7% and 7.8% of the aliskiren/amlodipine 300/10 mg, aliskiren/amlodipine 150/10 mg and amlodipine 10 mg groups, respectively). Of the 847 randomised patients, there were 843 (99.5%) in the FAS and 731 (86.3%) in the PPS, with similar proportions in the 3 treatment groups.

Baseline characteristics and medical history was comparable between treatment groups. The study population was 61.3% male and 99.4% Caucasian with a mean age of 54.6 years (18.1% aged ≥65 years). Nearly half (45.9%) of the patients were obese (BMI ≥30 kg/m^2), with 47.8% having metabolic syndrome and 15% diabetes. The mean duration of hypertension of 8.1 years and 1.9% of all patients were treatment naïve. Baseline BP was comparable between groups; msDBP ranged from 94.4 to 94.8 mmHg and msSBP ranged from 149.7 to 151.7 mmHg.

Primary outcome

The change from baseline in the LSM msDBP was -10.99, -8.95 and -7.23 mmHg for aliskiren/amlodipine 300/10 mg, aliskiren/amlodipine 150/10 mg and amlodipine 10 mg groups, respectively. Both aliskiren/amlodipine combinations resulted in a statistically significant (p≤0.0077) greater reduction in msDBP over the 8 week treatment period (FAS) compared to amlodipine 10 mg (-3.76 mmHg for 300/10 mg and -1.72 mmHg for 150/10 mg) (Table 11). In addition, aliskiren/amlodipine 300/10 mg resulted in a greater effect (-2.04 mmHg) than the aliskiren/amlodipine 150/10 mg dose. Results were similar with the PPS analysis.

Table 11: Study SPA2304 – Statistical analysis of change from baseline in msDBP at endpoint (FAS)

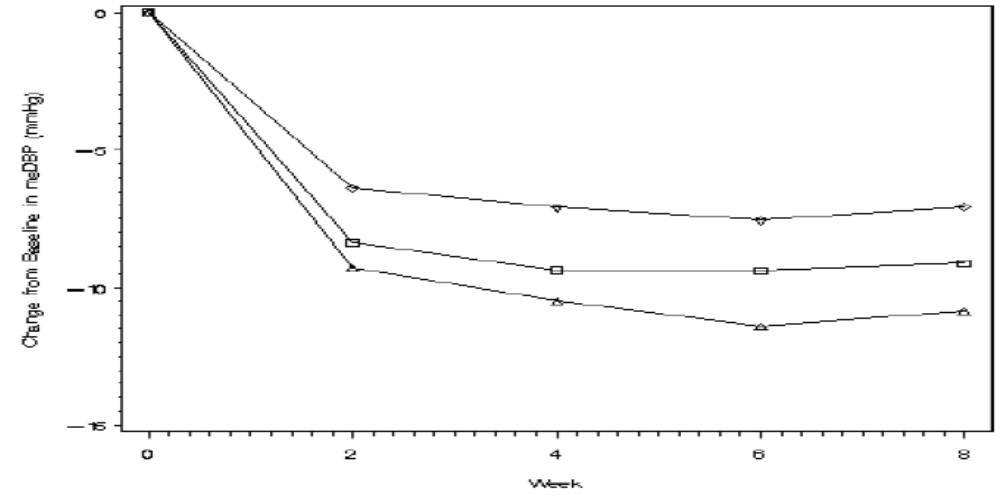
Treatment Group	N	LSM change from baseline (SE)		
Aliskiren/Amlodipine 300/10 mg	277	-10.99 (0.462)		
Aliskiren/Amlodipine 150/10 mg	281	-8.95 (0.460)		
Amlodipine 10mg	279	-7.23 (0.459)		
Pair wise Comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Aliskiren/amlodipine 300/10 mg vs. Amlodipine 10mg		-3.76 (0.644)	(-5.03, -2.50)	<0.0001*
Aliskiren/amlodipine 150/10 mg vs. Amlodipine 10mg		-1.72 (0.642)	(-2.98, -0.46)	0.0077*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval
Least square means, confidence intervals and p-values were from an ANCOVA model containing treatment, region and baseline.
* Indicates statistical significance at 0.05 level

Secondary Outcomes

A LSM change from baseline in msSBP of -14.42, -11.01 and -8.20 mmHg was found for the aliskiren/amlodipine 300/10 mg, aliskiren/amlodipine 150/10 mg and amlodipine 10 mg groups, respectively. There was also a statistically significant greater reduction in msSBP in the combination groups compared to amlodipine alone (p≤0.0033) (-6.22 mmHg for 300/10 mg and -2.81 mmHg for 150/10 mg). DBP and SBP reduction was seen at 2 weeks and was maintained to Week 8 (Figure 5).

Figure 5: Study SPA2304 – Average of change from baseline in msDBP by treatment group and visit (FAS)



Treatment: Aliskiren 300mg/Amlodipine 10mg
Aliskiren 300mg/Amlodipine 5mg
Aliskiren 300mg
Week 0 = Visit 5

Diastolic BP response (<90 mmHg or ≥10 mmHg reduction from baseline) was significantly greater in the aliskiren/amlodipine 300/10 mg compared to the amlodipine 10 mg group (81.6% vs 63.4%, p<0.0001) but not in the aliskiren/amlodipine 150/10 mg group (69.4% vs 63.4%, p=0.096). A response on systolic BP (<140 mmHg or ≥20 mmHg reduction from baseline) was significantly greater in the combination groups: 70.4%, 56.6% and 48.8% of the aliskiren/amlodipine 300/10 mg, aliskiren/amlodipine 150/10 mg and amlodipine 10 mg groups, respectively.

BP control rate (defined as msDBP <90 mmHg and msSBP <140 mmHg) was significantly greater with aliskiren/amlodipine 300/10 mg compared to amlodipine (58.8% vs 38.4%, p<0.0001) however was not greater for the lower combination dose of 150/10 mg (41.6% vs 38.4%, p=0.32).

Subgroup analysis found the higher dose combination (300/10 mg) resulted in greater reduction of msDBP and msSBP than amlodipine alone in those aged <65 years and ≥65 years, and in males and females. As in the overall population, the lower combination dose of 150/10 mg had less effect in these subgroups. There were too few non-Caucasians in the study to analyse by race.

Summary

In hypertensive patients who were inadequately controlled with amlodipine 10 mg monotherapy (msDBP ≥90 mmHg and <110 mmHg), the higher dose combination of aliskiren/amlodipine (300/10 mg) resulted in a statistically significant (p<0.0001) superior reduction in BP compared to amlodipine 10 mg after 8 weeks of treatment with a difference in the change from baseline of -6.22/-3.76 mmHg. The lower combination dose (150/10 mg) had a lower, though statistically significant (p≤0.0077), difference of -2.81/-1.72 mmHg. Reduction in BP was seen after 2 weeks of treatment and an incremental effect with the higher combination dose was again found. BP control rate for aliskiren/amlodipine 300/10 mg and 150/10 mg was 58.8% and 41.6% compared to 38.4% for amlodipine 10 mg and was only significantly greater for the higher combination dose. Likewise, diastolic BP response rate was only significantly improved with the higher

dose. These findings were consistent across subgroups of gender and age. Analysis by race was not possible due to low non-Caucasian numbers.

SPP2305 (short term amlodipine 5 mg controlled)

Methods

Study SPP2305 was a randomised, double blind, parallel group study in nonresponders to amlodipine 5 mg monotherapy. Unlike the previous studies, this study assessed the efficacy of aliskiren plus amlodipine, rather than the combination tablet. There was a 2 to 4 week wash out, a 4 week single blind run-in period on amlodipine 5 mg daily and a 6 week (rather than 8 week) double blind treatment period in which nonresponders to amlodipine were randomised to one of 3 groups: aliskiren 150 mg + amlodipine 5 mg; amlodipine 5 mg; and amlodipine 10 mg.

Objectives

The primary objective was to demonstrate efficacy of aliskiren 150 mg with amlodipine 5 mg in hypertensive patients who did not show sufficient BP response to a 4 week treatment of amlodipine 5 mg, with efficacy being a superior reduction in msDBP from baseline to end of study (6 weeks) when compared to amlodipine 5 mg. Secondary objectives included effect on msSBP, BP control rate, msDBP and msSBP response rates and safety.

Study participants

For inclusion non-treated patients needed to have an msDBP ≥95 mmHg and <110 mmHg and treated patients an msDBP <110 mmHg. For entry to the single blind period the msDBP needed to be ≥95 mmHg and <110 mmHg and for randomisation to double blind treatment needed to be ≥90 mmHg and <110 mmHg. Exclusion criteria were essentially the same as previous trials except for exclusion of diabetes with glycosylated haemoglobin (HbA1c) >9%, serum sodium < lower limit of normal (LLN), serum potassium <3.5 or ≥5.5 mmol/L, dehydration, and renal impairment with serum creatinine >2.0 mg/dL for men or >1.7 mg/dL for women.

Outcomes/endpoints

The primary efficacy variable was the change from baseline to end of study in msDBP at trough. The primary analysis population was the ITT population with LOCF.

Statistical Considerations

A sample size of 453 completed patients (151 per group) was needed to give the study a 90% power to detect a 3 mmHg difference in the change from baseline in msDBP assuming a SD of 8 mmHg and α=0.05. Allowing 10% drop-out, 504 patients need to be randomised. Patients were randomised in a 1:1:1 ratio using randomisation lists produced by the sponsor.

The primary analysis was a two way ANCOVA with treatment and region as factors and baseline msDBP as a covariate. The proportion of responders was analysed by logistic regression. The ITT population was all randomised patients who received at least one dose of double blind medication with at least one post-baseline efficacy measurement.

Results

The study was conducted in 2005 in 81 centres in Denmark, Germany, Greece, Slovakia, Korea, Malaysia, South Africa and US.

There were 762 subjects enrolled and 545 (71.5%) randomised with 187, 180 and 178 in the aliskiren 150 mg + amlodipine 5 mg, amlodipine 5 mg and amlodipine 10 mg groups,

respectively. For the 217 (28.5%) patients who discontinued at the single blind run-in period, 22.0% had abnormal procedure results including not meeting the BP criteria, 2.1% had AEs and 1.6% withdrew consent. There were 523/545 (96.0%) patients who completed the study and 22 (4.0%) who prematurely discontinued. Major protocol deviations occurred in 9.6%, 11.1% and 7.9% of the aliskiren 150 mg + amlodipine 5 mg, amlodipine 5 mg and amlodipine 10 mg groups, respectively. Of the 545 randomised patients, there were 541 (99.3%) in the ITT and 478 (87.7%) in the PPS, with similar proportions in the 3 treatment groups.

Baseline characteristics and medical history was comparable between treatment groups. The study population was 53.6% male, 69.4% Caucasian, 17.6% Black, 11.2% Asian, with a mean age of 53 years (17.8% aged ≥65 years), 44.6% were obese (BMI ≥30 kg/m^2) and 15% had diabetes. The mean duration of hypertension was 8 years. Baseline BP was comparable between groups; msDBP ranged from 95.7 to 96.5 mmHg and msSBP ranged from 150.5 to 150.8 mmHg. Concomitant medications were taken by 62.9% of patients with similar usage across the groups. The most frequently used medications were acetylsalicylic acid (12.5%), HMG CoA reductase inhibitors (16.0%), topical anti-inflammatories (11.0%) and anilides (10.3%).

Primary outcome

The change from baseline in the LSM msDBP was -8.46, -4.84 and -8.04 mmHg for aliskiren 150 mg + amlodipine 5 mg, amlodipine 5 mg and amlodipine 10 mg groups, respectively. The aliskiren 150 mg+amlodipine 5 mg resulted in a statistically significant (p<0.0001) greater reduction in msDBP over the 6 week treatment period compared to amlodipine 5 mg of -3.62 mmHg, however the difference compared to amlodipine 10 mg was not significant (-0.42 mmHg, p=0.617) (Table 12). Similar results were found on the PPS analysis. BP reduction was seen after one week and maximal by 3 weeks of treatment.

Table 12: Study SPA2303 – Statistical analysis of change from baseline in msDBP at double blind endpoint (ITT)

Treatment Group	N	LSM change from Baseline (SE)	
Aliskiren 150 mg + Amlodipine 5 mg	187	-8.46	(0.60)
Amlodipine 5 mg	177	-4.84	(0.62)
Amlodipine 10 mg	177	-8.04	(0.62)

Pairwise Comparison	LSM difference in change from Baseline (SE)		95% CI for LSM difference	p-Value
Aliskiren 150 mg + Amlodipine 5 mg vs. Amlodipine 5 mg	-3.62	(0.83)	(-5.25, -1.99)	<.0001*
Aliskiren 150 mg + Amlodipine 5 mg vs. Amlodipine 10 mg	-0.42	(0.83)	(-2.05, 1.21)	0.6167

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

Secondary Outcomes

A LSM change from baseline in msSBP of -10.98, -4.96 and -9.63 mmHg was found for aliskiren 150 mg+amlodipine 5 mg, amlodipine 5 mg and amlodipine 10 mg groups, respectively. The reduction in msSBP was significantly greater for aliskiren 150 mg+amlodipine 5 mg than amlodipine 5 mg (-6.02 mmHg, p<0.0001) and again was not significantly different compared to amlodipine 10 mg (-1.35 mmHg, p=0.267).

Diastolic BP response (<90 mmHg or ≥10 mmHg reduction from baseline) was significantly greater in the aliskiren 150 mg+amlodipine 5 mg compared to the amlodipine 5 mg (64.2% vs 45.2%, p=0.0005) but not compared to amlodipine 10 mg group (64.2% vs 59.9%, p=0.637). BP control rate (defined as endpoint BP <140/90 mmHg) was significantly greater with aliskiren 150 mg+amlodipine 5 mg compared to amlodipine 5

mg (42.8% vs 22.6%, p<0.0001) however was not greater than for amlodipine 10 mg (42.8% vs 37.8%, p=0.523).

Summary

In hypertensive patients who were inadequately controlled with amlodipine 5 mg monotherapy (msDBP ≥90 mmHg and <110 mmHg), the addition of aliskiren 150 mg resulted in a significant reduction in msSBP and msDBP of -6.0/-3.6 mmHg after 6 weeks of treatment. The effect on BP reduction was not, however, significantly different to amlodipine 10 mg (-1.35/-0.42 mmHg). Diastolic BP response rates (64.2% vs 45.2%) and BP control rates (42.8% vs 22.6%) were improved with the addition of aliskiren 150 mg to amlodipine 5 mg compared to amlodipine 5 mg monotherapy. However, this response was no greater than that seen with amlodipine 10 mg monotherapy.

Supportive studies

SPP2323 and extension SPP2323E1 (long term HCT controlled)

Methods

Study SPP2323 was a 26 week, randomised, double blind, parallel group, active controlled, dose titration study to evaluate the efficacy and safety of aliskiren (forced titration to 300 mg) compared to hydrochlorothiazide (HCT) (forced titration to 25 mg) with the optional addition of open label amlodipine, followed by a second 26 weeks of blinded treatment, in 1275 patients with essential hypertension. The study was conducted in 2005-2006 in Europe at 132 centres. There was a 2 week wash out period for patients on previous antihypertensive medication and a 2 to 4 week single blind run-in period to determine eligibility. Patients were then randomised in a 2:2:1 ratio to receive aliskiren, HCT or placebo and after 6 weeks, placebo patients were re-randomised to aliskiren or HCT in a 1:1 ratio. Aliskiren and HCT dose was 150 mg and 12.5 mg respectively with a forced titration after 3 weeks to 300 mg and 25 mg respectively. Down titration of these medications was not permitted. Patients not achieving target BP (<140/90 mmHg) were given open label amlodipine 5 mg which could be increased to 10 mg. No other antihypertensive medications were allowed.

Study participants

For inclusion, patients with essential hypertension needed to have msDBP ≥90 mmHg and <110 mmHg after washout (visit 2) and msDBP ≥95 mmHg and <110 mmHg at randomisation (visit 3) with ≤10 mmHg difference in msDBP from Visit 2. Exclusion criteria were essentially the same as previous trials.

Outcomes/endpoints

The primary efficacy variable was the change from baseline to 26 weeks in trough msDBP.

Statistical Considerations

Patients were randomised using an IVRS balanced by study centre. For the primary analysis, placebo subjects were pooled according to which treatment they were later reassigned. For assessment of non-inferiority of the aliskiren based regimen to HCT based regimen, the non-inferiority margin was a 2 mmHg reduction in msDBP with a one-sided significance level of 0.025. The non-inferiority margin for msSBP was 4 mmHg. Tests used an ANCOVA model with regimen and country as factors and baseline msDBP as covariate. Logistic regression was used for responder and BP control analysis. The ITT population with LOCF was used for the primary analysis. The per protocol population at Week 26 (PP-26) and Week 52 (PP-52) included all ITT patients completing this period without any major protocol deviations.

Results

There were 1440 patients screened: 1275 enrolled in the single blind period and 1124 randomised (with 221 receiving placebo during the first 6 weeks). Overall, 978 (87%) completed 26 weeks, 965 entered the extension phase, and 918 (81.7%) completed 52 weeks of treatment.

Groups were comparable and the mean age was 56 years and overall 99% were Caucasian, 55.1% male, 35.2% obese, 10.9% diabetic, 42.5% had metabolic syndrome and the mean duration of hypertension was 7 years. Baseline BP was comparable with msDBP 98.9-99.0 mmHg and msSBP 154.1-154.3 mmHg.

The study found a reduction in msDBP and msSBP with aliskiren 300 mg that was non-inferior (2 mmHg non-inferiority margin) to HCT at 26 and 52 weeks and similar BP control rates (msBP <140/90 mmHg) (67.3% vs 64.0% at Week 26 and 69.9% vs 63.5% at Week 52 in the aliskiren and HCT groups, respectively). At Week 52, there were 47.5% and 52.5% of patients in the aliskiren and HCT groups respectively taking add-on amlodipine (including 20% and 23.3% taking amlodipine 10 mg).

Evaluator Comment

While in patients dosed with aliskiren 300 mg nearly half (47.5%) ended up taking optional add-on amlodipine after 52 weeks of treatment, analysis of this subgroup of patients was not undertaken in the sponsor's *Clinical Study Report*. As this study did not directly assess the efficacy of the combination of aliskiren and amlodipine, the efficacy results of this study are not directly relevant. The utility of the data is from a safety perspective which is discussed later.

SPA2301 (long term uncontrolled)

Methods

Study SPA2301 was a 54 week, open label, multicentre study assessing the long term safety of the combination aliskiren/amlodipine 300/10 mg in patients with essential hypertension. After a 1 to 4 week washout there was a 54 week open label treatment period. In the first 2 weeks treatment was aliskiren/amlodipine 150/5 mg which was then force titrated to aliskiren/amlodipine 300/10 mg for the next 52 weeks. After 72 days of treatment, patients with a msSBP ≥140 mmHg and/or msDBP ≥90 mmHg for two consecutive visits could have optional add-on hydrochlorothiazide (HCT) 12.5 mg with an increase to 25 mg if BP remained elevated. Down titration of medications was not allowed. The study drug was discontinued if: msDBP ≥110 mmHg or msSBP ≥180 mmHg; if there was symptomatic hypotension or msDBP <60 mmHg or msSBP <100 mmHg; or if serum potassium was >5.5 mEq/L on a repeated sample.

Objectives

The primary objective of the study was long term safety, secondary objectives included evaluation of long term BP lowering efficacy, BP control rates and msDBP response rates.

Study participants

Inclusion criteria were: ≥18 years; essential hypertension with msDBP ≥90 mmHg and <110 mmHg (at Visit 1 and 2 for newly diagnosed, or after 2 to 4 weeks washout for previously treated patients). Exclusion criteria were the same as SPA2305.

Outcomes/endpoints

Efficacy endpoints were secondary and included the change from baseline in msDBP, msSBP, blood pressure control (msSBP/msDBP <140/90 mmHg) and msDBP response (msDBP <90 mmHg or a ≥10mmHg decrease from baseline). Efficacy was assessed on the

treated population of all patients who took at least one dose of study medication with LOCF.

Statistical Considerations

The sponsor stated the sample size of 500 patients was selected to meet ICH guideline requirements of data in more than 300 patients for 6 months and more than 100 patients for 12 months at high dose, assuming a discontinuation rate of 20% in the first 6 months and 30% in the second 6 months. The study was open label and not randomised. As this was a single group study, only summary statistics were provided.

Results

The study was conducted between 2006-2008 at 89 centres in Belgium, Switzerland, Germany, Denmark, Finland, Iceland, India and the USA.

There were 652 patients who entered the washout and 556 (85.3%) continued onto study treatment. Discontinuations during washout (14.7%) were mainly for abnormal test procedures (9.4%) and consent withdrawal (2.3%). There were 452/556 (81.3%) patients who completed 12 months of treatment and 104/556 (18.7%) who prematurely discontinued, 12.1% were for AEs and 2.3% withdrew consent. Peripheral oedema was the most frequent AE leading to discontinuation (6.5%). Protocol deviations occurred in 26.1% of patients with most relating to use of prohibited concomitant medications (7.9% systemic corticosteroids, 6.7% medications for hypertension) and 2.0% not meeting inclusion/exclusion criteria.

Of the 556 treated patients, 470 (84.5%) received aliskiren/amlodipine and 86 (15.5%) received aliskiren/amlodipine plus add-on HCT at some time during the study. The average age was 54.4 (range: 21 to 88) years, 18.2% were ≥65 years, 59.4% were male, 48.7% had a BMI ≥30 kg/m^2, 42.6% had metabolic syndrome and the mean duration of hypertension was 8.1 years. The patients who received add-on HCT were more likely to have metabolic syndrome (60.5% vs 39.4%), be obese (64% vs 46%) and have longer duration of hypertension (10.2 years vs 7.7 years). The msDBP and msSBP were 97.6 and 153.5 mmHg, respectively. Baseline BP in those who received add-on HCT was slightly higher than in the aliskiren/amlodipine alone group. The most frequent medical conditions at baseline (by primary System Organ Class [SOC] were *Metabolism and Nutrition Disorders* (49.6%), *Musculoskeletal and Connective Tissue Disorders* (42.8%), *Surgical and Medical Procedures* (30.6%), *Gastrointestinal Disorders* (28.1%), *Psychiatric Disorders* (22.1%), and *Nervous System Disorders* (20.3%). The most frequent diagnoses were hypercholesterolaemia (18.2%) and hyperlipidaemia (16.2%).

Secondary outcomes

The msDBP started to reduce at Week 2 with the aliskiren/amlodipine 150/5 mg dose (mean reduction -8.3 mmHg) and a maximal reduction (-15.1 mmHg) was seen by Week 10 after 8 weeks of the forced titration to aliskiren/amlodipine 300/10 mg. This reduction was maintained to the study end at Week 54 (mean reduction -15.5 mmHg) (Table 13, Figure 6). The reduction in msSBP commenced within 2 weeks of treatment, and was maximal at Week 28 (mean reduction -25.9 mmHg) and was also maintained to the study end (-24.2 mmHg) (Figure 6). The addition of HCT showed an added reduction in msDBP and msSBP.

Table 13: Study SPA2301 – Summary statistics for the change from baseline (Visit 4) in msDBP by Visit (treated population)

Week (Visit)	Aliskiren/Amlodipine* N = 470		Aliskiren/Amlodipine /HCTZ** N = 86		Total N = 556	
	N***	Mean (SD)	N***	Mean (SD)	N***	Mean (SD)
Week 2 (Visit 5)	467	-8.7 (6.94)	86	-5.9 (6.05)[a]	553	-8.3 (6.89)
Week 4 (Visit 6)	459	-14.0 (6.88)	85	-11.9 (5.58)[a]	544	-13.7 (6.73)
Week 6 (Visit 7)	453	-15.7 (6.96)	86	-11.5 (7.36)[a]	539	-15.1 (7.19)
Week 10 (Visit 8)	440	-16.3 (6.69)	86	-9.3 (7.22)[a]	526	-15.1 (7.24)
Week 14 (Visit 9)	429	-17.1 (6.84)	85	-13.1 (7.64)	514	-16.4 (7.12)
Week 28 (Visit 10)	416	-16.7 (7.15)	81	-14.7 (8.22)	497	-16.4 (7.36)
Week 41 (Visit 11)	396	-17.0 (7.26)	75	-15.4 (6.86)	471	-16.8 (7.21)
Week 54 (Visit 12)	383	-16.3 (7.13)	74	-15.3 (6.55)	457	-16.1 (7.04)
Endpoint****	467	-15.7 (7.61)	86	-14.2 (7.90)	553	-15.5 (7.67)

*'Aliskiren /Amlodipine' is the group of patients who took only Aliskiren/Amlodipine (without HCTZ) throughout the study.

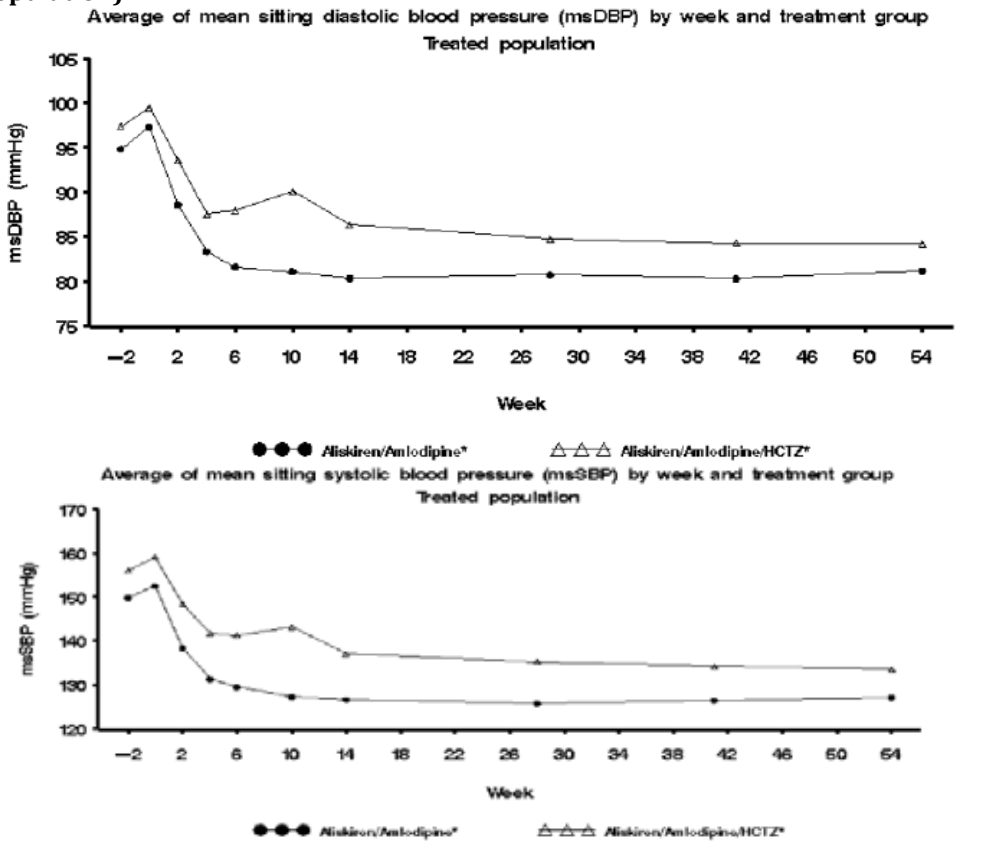
**'Aliskiren /Amlodipine/HCTZ' is the group of patients who took HCTZ at some time during the study (HCTZ was only added to eligible patients after visit 8).

*** N*** is the total number of patients with msDBP observations at both baseline and post-baseline visits.

a: Use of HCTZ was not permitted until after week 10 (visit 8).

**** Endpoint is the value at Week 54 (visit 12) or last observation carried forward (LOCF) based on the availability of measurements.

Figure 6: Study SPA2301 – Average of msDBP and msSBP by week (treated population)



* 'Aliskiren/Amlodipine' is the group of patients who took only Aliskiren/Amlodipine (without HCTZ) throughout the study.
'Aliskiren/Amlodipine/HCTZ' is the group of patients who took HCTZ at some time during the study.
— Week 0 (day 1) = Visit 4.

Note: Addition of HCTZ was permitted for qualifying patients after Week 10.

The proportion of patients with BP control (msSBP/msDBP <140/90 mmHg) was 74.3% overall, 77.3% for those on aliskiren/amlodipine and 58.1% for those on aliskiren/amlodipine plus HCT. A response on msDBP of <90 mmHg or ≥10 mmHg reduction from baseline was achieved in 89.7% of patients. Efficacy was seen across all subgroups of gender, age (±65 years) and race (Caucasian, Black, Asian).

Biomarkers

A subset of patients had high sensitivity C-reactive protein (hsCRP), plasma renin activity (PRA), and plasma aldosterone measured at baseline and at study end (aliskiren/amlodipine n=274; aliskiren/amlodipine/HCT n=55). PRA decreased by 70% overall and there was little effect on plasma aldosterone or hsCRP which is consistent with the mechanism of action.

Summary

In this open label study of 556 patients with essential hypertension, the combination aliskiren/amlodipine 300/10 mg (including 15.5% who also received HCT) resulted in a BP control rate of 74% and a long term msDBP and msSBP reduction of -15.5 mmHg and -24.2 mmHg respectively. A DBP response (<90 mmHg or ≥10 mmHg reduction from baseline) was noted in 89.7% of patients. The addition of HCT resulted in further BP reduction in those inadequately controlled with aliskiren/amlodipine alone. Efficacy was seen across all subgroups.

Evaluators overall conclusions on clinical efficacy

The clinical program included 5570 hypertensive patients, 2835 of whom received at least one dose of aliskiren/amlodipine combination and 612 who received the combination for at least 6 months. There were 7 main clinical studies: one short term, placebo controlled (SPA2305); 3 short term, active controlled (SPA2303, SPA2304 and SPP2305); 1 long term controlled (SPP2323 and its extension study SPP2323E1); and one long term uncontrolled (SPA2301). The combination tablet was used in all studies except for SPP2305 where aliskiren 150 mg and amlodipine 5 mg were given separately, and SPP2323 which assessed aliskiren 300 mg (versus HCT) with optional add-on amlodipine.

The trials enrolled a population with mild to moderate hypertension. The placebo-controlled trial required an msDBP of 95–109 mmHg at the end of the placebo run-in before randomisation; the nonresponder studies required an msDBP of 90-109 mmHg after the 4 week monotherapy run-in; and the open label long term study required an msDBP of 90-109 mmHg after washout. Patients were excluded if they had severe hypertension (msDBP ≥110 mmHg and/or msSBP ≥180 mmHg), secondary hypertension, evidence of significant hepatic or renal impairment, heart failure, diabetes with poor glucose control, a history of myocardial infarction, cerebrovascular accident, or significant gastrointestinal disease or surgery. Controlled studies had populations that were well balanced between treatment groups. Analysis used the FAS which excluded misrandomised patients (except SPP2305 which used the ITT population).

The studies in the submission were designed in accordance with the relevant TGA-adopted EU guidelines on development of antihypertensives and fixed combination products.[14,15] This included appropriate BP measurements, an adequate run-in period of 2 to 4 weeks,

[14] EMEA, Committee for Medicinal Products for Human Use (CHMP), 23 June 2004. Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, CPMP/EWP/238/95 Rev 2.

[15] EMEA, Committee for Medicinal Products for Human Use (CHMP), 19 February 2009. Guideline on Clinical Development of Fixed Combination Medicinal Products, CPMP/EWP/240/95 Rev 1.

treatment duration of 8 weeks (except for SPP2305 which was 6 weeks), the use of randomisation, blinding, placebo controls and a factorial design to allow simultaneous comparisons of various dosage combinations with the monotherapies and placebo.

SPA2305 was the pivotal efficacy study which randomised 1688 patients. In this study there was a high rate of obesity (46%) and metabolic syndrome (46%), and 11% had diabetes. After 8 weeks of treatment, the combination of aliskiren/amlodipine (doses of 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg) resulted in statistically significant and clinically meaningful reductions in msDBP compared to the respective monotherapies (differences of -2.3 to -8.2 mmHg). Reduction in msSBP was also seen with the 150/5 mg and 300/5 mg doses, while combinations with 10 mg amlodipine did not produce a greater SBP reduction than amlodipine 10 mg monotherapy. BP control (<140/90 mmHg) was significantly greater with the combinations than the monotherapies with greatest control (68.3%) seen with aliskiren/amlodipine 300mg/10mg and this compared to 50.3% with amlodipine 10 mg. The effect on BP reduction was seen after 1 week of treatment and was maximal at 4 weeks. There was also a significant reduction in mean 24 hour ambulatory DBP and SBP and the effect was maintained over the 24 hour period with once daily dosing. The combination therapies were effective across subgroups of gender and age, though there were too few blacks to draw conclusions on this racial group.

In the three active controlled studies, patients were inadequately controlled (msDBP ≥90 mmHg and <110 mmHg) on monotherapy with either aliskiren 300 mg (SPA2303) or amlodipine 10 mg (SPA2304) or amlodipine 5 mg (SPP2305). In study SPA2303, involving hypertensive patients who were inadequately controlled with aliskiren 300 mg, the combination of aliskiren/amlodipine (300/10 mg and 300/5 mg) resulted in a statistically significant ($p<0.0001$) superior reduction in BP compared to aliskiren 300mg after 8 weeks of treatment. The difference in the change from baseline in msDBP was -7.23 mmHg and -4.71 mmHg and in msSBP it was -11.62 mmHg and -8.01 mmHg for 300/10 mg for 300/5 mg groups, respectively, which is clinically meaningful. An incremental improvement in BP reduction with the 300/10 mg dose over the 300/5 mg dose was also noted. There was also a significantly greater BP control rate (65.5% and 56.6% for 300/10 mg and 300/5 mg groups, respectively) compared with aliskiren alone (31.5%). The greater BP reduction was consistent across subgroups of age, gender and race (Caucasian and Asian).

SPA2304 examined patients who were inadequately controlled with amlodipine 10 mg and found the higher dose combination of aliskiren/amlodipine (300/10 mg) resulted in a statistically significant ($p<0.0001$) superior reduction in BP compared to amlodipine after 8 weeks of treatment (the difference in the change from baseline in msDBP and msSBP was -3.76 and -6.22 mmHg). The lower combination dose (150/10 mg) had a lower (though statistically significant $p\leq0.0077$), difference in msDBP and msSBP of -1.72 mmHg and -2.81 mmHg, respectively. Reduction in BP was seen after 2 weeks of treatment and an incremental effect with the higher combination dose was again found. BP control rate for aliskiren/amlodipine 300/10 mg and 150/10 mg was 58.8% and 41.6% compared to 38.4% for amlodipine 10 mg and was only significantly greater for the higher combination dose. Likewise, diastolic BP response was only significantly improved with the higher dose. These findings were consistent across subgroups of gender and age. Analysis by race was not possible due to low non-Caucasian numbers.

In SPP2305, when aliskiren 150 mg was added to amlodipine 5 mg a significant reduction in msSBP and msDBP of -6.0/-3.6 mmHg was noted after 6 weeks of treatment (ITT population with LOCF). The effect on BP reduction was not, however significantly different to amlodipine 10 mg (-1.35/-0.42 mmHg). Diastolic BP response rates and BP control rates were improved (64.2% vs 45.2% and 42.8% vs 22.6% respectively) with the

addition of aliskiren 150 mg to amlodipine 5 mg compared to amlodipine 5 mg monotherapy. There was, however, no greater response compared to amlodipine 10 mg monotherapy (BP control rate 42.8% vs 37.8% p=0.52).

The 3 active controlled studies demonstrated an incremental increase in BP reduction with the combination product compared to the monotherapy as summarised in Table 14.

Table 14: Incremental msDBP and msSBP reduction from baseline at endpoint for aliskiren/amlodipine combination over monotherapies

		LS mean difference in change from baseline					
		msDBP (mmHg) (primary efficacy)			msSBP (mmHg) (secondary efficacy)		
Treatment comparison (mg)		A2303	A2304	P2305	A2303	A2304	P2305
Ali/aml 300/10	vs. ali 300	-7.23 *			-11.62 *		
Ali/aml 300/5	vs. ali 300	-4.71 *			-8.01 *		
Ali/aml 300/10	vs. aml 10		-3.76 *			-6.22 *	
Ali/aml 150/10	vs. aml 10		-1.72 *			-2.81 *	
Ali/aml 150/5	vs. aml 5			-3.62 *			-6.02 *
Ali/aml 150/5	vs. aml 10			-0.42			-1.35

* Indicates statistical significance at 0.05 level

For Study SPA2303, N includes patients who had baseline and post-baseline measurements. Three patients (1 in aliskiren/amlodipine 300/10 mg and 2 in aliskiren/amlodipine 300/5 mg) were excluded from the analysis due to lack of post-baseline assessment.

Likewise, the improvement in BP control rate with the combination therapy compared to the monotherapy is summarised in Table 15.

Table 15: Blood pressure control rates (%) at endpoint

Study	Treatment comparison (mg) A	vs. B	Treatment A	Treatment B	p-value
SPA2303	Ali/aml 300/10	vs. ali 300	65.5%	31.5%	<0.0001*
	Ali/aml 300/5	vs. ali 300	56.6%	31.5%	<0.0001*
SPA2304	Ali/aml 300/10	vs. aml 10	58.8%	38.4%	<0.0001*
	Ali/aml 150/10	vs. aml 10	41.6%	38.4%	0.3248
SPP2305	Ali/aml 150/5	vs. aml 5	42.78%	22.60%	<0.0001*
	Ali/aml 150/5	vs. aml 10	42.78%	37.85%	0.5229

BP control = msSBP <140 mmHg and msDBP <90 mmHg

The percentage of patients with BP control was analyzed using a logistic-regression model with treatment and region as factors and baseline msDBP as a covariate. Baseline was the Day 1 value.

In Study SPA2303, 3 patients (1 in aliskiren/amlodipine 300/10 mg group and 2 in aliskiren/amlodipine 300/5 mg group) were excluded from the analysis due to lack of post-baseline assessment.

* Indicates statistical significance at 0.05 level.

N includes patients who had both baseline and post-baseline measurements.

There were 2 long term studies: one controlled 52 week study (SPP2323) and one open label 54 week study (SPA2301). SPP2323 was a comparison study of aliskiren 300 mg with HCT 25 mg with optional add-on amlodipine (5 or 10 mg) in 1124 patients with mild to moderate essential hypertension. While in patients dosed with aliskiren 300 mg nearly half (47.5%) ended up taking optional add-on amlodipine after 52 weeks of treatment, analysis of this subgroup of patients was not provided in the sponsor's *Clinical Study Report*. While this study did not provide efficacy data for the aliskiren/amlodipine combination, the safety data was relevant and is presented below.

SPA2301 found that in 556 patients with essential hypertension after 54 weeks of treatment, the combination aliskiren/amlodipine 300/10 mg (including 15.5% who also received add-on HCT) resulted in a BP control rate of 74% and a long term msDBP and msSBP reduction of -15.5 mmHg and -24.2 mmHg respectively. A DBP response (<90 mmHg or ≥10 mmHg reduction from baseline) was noted in 89.7% of patients. The addition of HCT resulted in further BP reduction in those inadequately controlled with

aliskiren/amlodipine alone. Efficacy was seen across subgroups, although there were only 101 patients aged ≥65 years.

The long term studies demonstrated sustained reduction in BP over the treatment period of up to 54 weeks with no evidence of tolerance resulting in loss of efficacy. Effects on treatment cessation were not assessed in the development program of the combination therapy and, as neither product information for aliskiren or amlodipine mention withdrawal effects or rebound hypertension, the evaluator agreed with the sponsor that such assessment is not necessary.

Subgroup analyses conducted in the individual studies found that the BP lowering was consistent across groups. While the majority of study participants were aged <65 years of age, BP reduction and control rates were similar in those under and over 65 years. The number of patients ≥75 years or with BMI <20 kg/m^2 were too small for meaningful conclusions to be made. There were no notable findings in the different racial groups, though the numbers of non-Caucasians were low. Females were well represented in the studies and efficacy was similar in the genders in short term and the long term studies. The clinical program excluded patients with severe hypertension, secondary hypertension, or with high cardiovascular risk such as post MI, so no efficacy conclusion can be drawn in these populations.

Once daily dosing was supported by efficacy results from measurements taken at trough approximately 24 h post dose and from the ABPM results which demonstrated BP reduction over the 24 h period of monitoring.

Safety

Introduction

Safety assessments included monitoring of AEs and serious adverse events (SAEs), vital signs, physical examination, haematology and biochemistry assessments. The study population was males and females 18 years of age or more with mild to moderate hypertension. Patients with severe hypertension, unstable diabetes, pregnancy, and those with significant cardiac or gastrointestinal disease were excluded. Where doses were titrated, safety data was presented by the final titrated dose received. The safety data was evaluated in 4 groups:

- Group A - the short term, placebo controlled study SPA2305 (n=1685, 724 fixed combination);
- Group B - all short term studies, SPA2305, SPA2303, SPA2304 and SPP2305 (n=3890, 2031 fixed combination);
- Group C - long term, open label study SPA2301 (n=556 fixed combination);
- Group D - long term, controlled study SPP2323 and SPP2323E1 (n=1103, 248 aliskiren with add-on amlodipine).

Patient exposure

Safety data was collected from 5549 patients: 1685 in the short-term, placebo controlled study; 2205 in the short term, active controlled studies; 556 in the long term, open label study; and 1103 in the long term, active controlled studies. There were also 5 clinical pharmacology studies in 361 healthy subjects and 6 ongoing studies in hypertensive patients. There were 2835 patients who received at least one dose of aliskiren/amlodipine combination and 612 who were exposed for 6 months and 372 for 12 months. The total exposure by dose was 69.8, 69.5, 173.3, and 585.1 person years for the

aliskiren/amlodipine 150/5 mg, 150/10 mg. 300/5 mg and 300/10 mg dose combinations, respectively.

In the short term studies, median exposure was 56 days except, as SPP2305 was 6 weeks duration, in group B the aliskiren/amlodipine 150/5 mg group had a median exposure of 47 days and monotherapy amlodipine was 55 days. In group C, 405 patients were treated with aliskiren/amlodipine 300/10 mg for at least 6 months (180 days) and 292 for at least 12 months (360 days). There were 86/556 patients who received add-on HCT. In group D, there were 200 patients treated with aliskiren with add-on amlodipine for at least 6 months (180 days) and 125 for 9 months (270 days) with 156.2 patient years of exposure.

Adverse Events

In healthy volunteers in the pharmacology studies aliskiren/amlodipine was well tolerated with headache being the most frequent AE.

In group A (SPA2305) the rate of AEs was highest in the aliskiren/amlodipine 300/10 mg group (44.6%) compared to 31.4 to 37.0% in the other active groups and 37.4% in the placebo group (Table 16). Peripheral oedema was the most frequently reported AE and occurred in 13.6% and 13.8% of the aliskiren/amlodipine 300/10 mg and amlodipine 10 mg groups, respectively. Rates of peripheral oedema were lower in the other groups of aliskiren/amlodipine 150/10 mg (7.7%), aliskiren/amlodipine 150/5 mg (2.2%), aliskiren/amlodipine 300/5 mg (1.1%), amlodipine 5 mg (4.3%) and placebo (1.0%).

Table 16: Number (%) of patients with most frequent AEs (at least 2% for any treatment group) by preferred term, Group A

Preferred term	Placebo N=198 n (%)	Ali 150 mg N=194 n (%)	Ali 300 mg N=203 n (%)	Mono Ali N=397 n (%)	Aml 5 mg N=185 n (%)	Aml 10 mg N=181 n (%)	Mono Aml N=366 n (%)
Any AE	74 (37.4)	65 (33.5)	65 (32.0)	130 (32.7)	58 (31.4)	67 (37.0)	125 (34.2)
Edema peripheral	2 (1.0)	2 (1.0)	3 (1.5)	5 (1.3)	8 (4.3)	25 (13.8)	33 (9.0)
Headache	20 (10.1)	13 (6.7)	15 (7.4)	28 (7.1)	11 (5.9)	8 (4.4)	19 (5.2)
Upper respiratory tract infection	5 (2.5)	6 (3.1)	2 (1.0)	8 (2.0)	0 (0.0)	2 (1.1)	2 (0.5)
Cough	2 (1.0)	1 (0.5)	1 (0.5)	2 (0.5)	3 (1.6)	2 (1.1)	5 (1.4)
Dizziness	3 (1.5)	5 (2.6)	6 (3.0)	11 (2.8)	4 (2.2)	1 (0.6)	5 (1.4)
Dyslipidaemia	5 (2.5)	1 (0.5)	3 (1.5)	4 (1.0)	2 (1.1)	3 (1.7)	5 (1.4)
Nasopharyngitis	6 (3.0)	3 (1.5)	9 (4.4)	12 (3.0)	7 (3.8)	2 (1.1)	9 (2.5)
Fatigue	0 (0.0)	4 (2.1)	0 (0.0)	4 (1.0)	2 (1.1)	3 (1.7)	5 (1.4)
Back pain	3 (1.5)	2 (1.0)	3 (1.5)	5 (1.3)	3 (1.6)	1 (0.6)	4 (1.1)
Influenza	3 (1.5)	4 (2.1)	4 (2.0)	8 (2.0)	1 (0.5)	2 (1.1)	3 (0.8)
Diarrhea	1 (0.5)	7 (3.6)	2 (1.0)	9 (2.3)	2 (1.1)	2 (1.1)	4 (1.1)
Insomnia	2 (1.0)	2 (1.0)	2 (1.0)	4 (1.0)	1 (0.5)	1 (0.6)	2 (0.5)
Hyperlipidemia	3 (1.5)	2 (1.0)	0 (0.0)	2 (0.5)	0 (0.0)	4 (2.2)	4 (1.1)

Preferred term	Ali/Aml 150/5 mg N=181 n (%)	Ali/Aml 150/10 mg N=181 n (%)	Ali/Aml 300/5 mg N=178 n (%)	Ali/Aml 300/10 mg N=184 n (%)	All Ali/Aml N=724 n (%)
Any AE	60(33.1)	59(32.6)	57(32.0)	82(44.6)	258(35.6)
Edema peripheral	4(2.2)	14(7.7)	2(1.1)	25(13.6)	45(6.2)
Headache	11(6.1)	8(4.4)	6(3.4)	5(2.7)	30(4.1)
Upper respiratory tract infection	7(3.9)	5(2.8)	5(2.8)	4(2.2)	21(2.9)
Cough	4(2.2)	3(1.7)	1(0.6)	4(2.2)	12(1.7)
Dizziness	2(1.1)	2(1.1)	5(2.8)	3(1.6)	12(1.7)
Dyslipidaemia	5(2.8)	2(1.1)	2(1.1)	3(1.6)	12(1.7)
Nasopharyngitis	3(1.7)	4(2.2)	1(0.6)	3(1.6)	11(1.5)
Fatigue	1(0.6)	3(1.7)	2(1.1)	4(2.2)	10(1.4)
Back pain	0(0.0)	1(0.6)	3(1.7)	5(2.7)	9(1.2)
Influenza	1(0.6)	3(1.7)	2(1.1)	2(1.1)	8(1.1)
Diarrhea	1(0.6)	0(0.0)	4(2.2)	2(1.1)	7(1.0)
Insomnia	0(0.0)	4(2.2)	2(1.1)	0(0.0)	6(0.8)
Hyperlipidemia	1(0.6)	1(0.6)	0(0.0)	0(0.0)	2(0.3)

Preferred terms are sorted in descending frequency, as reported in the All Ai/Aml column.

Headache occurred in 4.1% of all aliskiren/amlodipine patients compared to 10.1% of the placebo group, 7.1% of aliskiren monotherapy and 5.2% of amlodipine monotherapy. Diarrhoea occurred in 0.0 to 2.2% of aliskiren/amlodipine combination groups compared to 3.6% of aliskiren 150 mg, 1.0% aliskiren 300 mg and 0.5% placebo groups. There were no notable differences between groups for dizziness and cough, both of which occurred in 1.7% of all aliskiren/amlodipine subjects.

In group B (short term studies) the AE incidence with aliskiren/amlodipine was similar to the component monotherapy groups. Again peripheral oedema was the most frequent AE occurring in 5.9% and 8.4% of the all aliskiren/amlodipine and amlodipine monotherapy groups, respectively (Table 17). Peripheral oedema was also found to be more frequent in women than men (7.6% vs 4.5%) treated with aliskiren/amlodipine. Dizziness, which was slightly more frequent in aliskiren 300 mg treated patients (1.8% aliskiren/amlodipine 300/5 mg, 1.7% aliskiren/amlodipine 300/10 mg) compared to placebo (1.5%) was not greater than aliskiren monotherapy (2.1%).

Table 17: Number (%) of patients with most frequent AEs (at least 2% for any treatment group) by preferred term, Group B

Preferred term	Placebo N=198 n (%)	Mono Ali N=657 n (%)	Mono Aml N=1004 n (%)	Ali/Aml 150/5 mg N=368 n (%)	Ali/Aml 150/10 mg N=464 n (%)	Ali/Aml 300/5 mg N=454 n (%)	Ali/Aml 300/10 mg N=745 n (%)	All Ali/Aml N=2031 n (%)
Any AE	74(37.4)	189(28.8)	323(32.2)	119(32.3)	158(34.1)	137(30.2)	254(34.1)	668(32.9)
Edema peripheral	2(1.0)	6(0.9)	84(8.4)	8(2.2)	37(8.0)	8(1.8)	66(8.9)	119(5.9)
Nasopharyngitis	6(3.0)	15(2.3)	26(2.6)	4(1.1)	19(4.1)	8(1.8)	25(3.4)	56(2.8)
Headache	20(10.1)	38(5.8)	36(3.6)	16(4.3)	11(2.4)	15(3.3)	11(1.5)	53(2.6)
Upper respiratory tract infection	5(2.5)	10(1.5)	6(0.6)	9(2.4)	6(1.3)	7(1.5)	9(1.2)	31(1.5)
Dizziness	3(1.5)	14(2.1)	13(1.3)	4(1.1)	4(0.9)	8(1.8)	13(1.7)	29(1.4)

Preferred terms are sorted in descending frequency, as reported in the All Ai/Aml column.

In group C (open label long term), peripheral oedema occurred in 22.7% of patients, dizziness in 5.4%, diarrhoea in 3.2% (including 2 SAEs of diarrhoea), cough 2.5% and orthostatic hypotension 0.5%. (Table 18). There were no cases of angioedema.

Table 18: Number (%) of patients with most frequent AEs (at least 2% for any treatment group) by preferred term, Group C

Preferred term	Ali/Aml 150/5 mg * N=556 n (%)	Ali/Aml 300/10 mg N=546 n (%)	All Ali/Aml N=556 n (%)	All Ali/Aml/HCTZ N=86 n (%)	Total N=556 n (%)
Any AE	131(23.6)	389(71.2)	413(74.3)	49(57.0)	424(76.3)
Edema peripheral	8(1.4)	108(19.8)	114(20.5)	12(14.0)	126(22.7)
Headache	19(3.4)	19(3.5)	37(6.7)	3(3.5)	38(6.8)
Upper respiratory tract infection	5(0.9)	32(5.9)	37(6.7)	5(5.8)	40(7.2)
Bronchitis	3(0.5)	27(4.9)	30(5.4)	4(4.7)	34(6.1)
Influenza	5(0.9)	24(4.4)	29(5.2)	2(2.3)	31(5.6)
Dizziness	5(0.9)	24(4.4)	28(5.0)	2(2.3)	30(5.4)
Nasopharyngitis	6(1.1)	22(4.0)	26(4.7)	1(1.2)	27(4.9)
Back pain	3(0.5)	22(4.0)	25(4.5)	3(3.5)	28(5.0)
Arthralgia	2(0.4)	22(4.0)	24(4.3)	1(1.2)	25(4.5)
Sinusitis	4(0.7)	17(3.1)	21(3.8)	1(1.2)	22(4.0)
Joint swelling	1(0.2)	16(2.9)	17(3.1)	0(0.0)	17(3.1)
Diarrhea	3(0.5)	13(2.4)	15(2.7)	3(3.5)	18(3.2)
Fatigue	9(1.6)	6(1.1)	15(2.7)	0(0.0)	15(2.7)
Cough	3(0.5)	11(2.0)	13(2.3)	1(1.2)	14(2.5)
Nausea	4(0.7)	9(1.6)	13(2.3)	2(2.3)	15(2.7)
Vertigo	4(0.7)	9(1.6)	13(2.3)	0(0.0)	13(2.3)
Musculoskeletal pain	0(0.0)	12(2.2)	12(2.2)	0(0.0)	12(2.2)
Pain in extremity	1(0.2)	11(2.0)	12(2.2)	2(2.3)	13(2.3)
Palpitations	3(0.5)	9(1.6)	12(2.2)	0(0.0)	12(2.2)
Urinary tract infection	2(0.4)	10(1.8)	12(2.2)	1(1.2)	13(2.3)
Gastroenteritis	0(0.0)	11(2.0)	11(2.0)	1(1.2)	12(2.2)
Osteoarthritis	2(0.4)	9(1.6)	11(2.0)	0(0.0)	11(2.0)
Conjunctivitis	1(0.2)	9(1.6)	10(1.8)	1(1.2)	11(2.0)
Viral infection	0(0.0)	9(1.6)	9(1.6)	2(2.3)	10(1.8)
Abdominal pain upper	0(0.0)	8(1.5)	8(1.4)	2(2.3)	10(1.8)
Dyspepsia	3(0.5)	6(1.1)	8(1.4)	3(3.5)	10(1.8)
Muscle spasms	1(0.2)	5(0.9)	6(1.1)	5(5.8)	11(2.0)
Tachycardia	2(0.4)	3(0.5)	4(0.7)	2(2.3)	6(1.1)
Joint sprain	0(0.0)	3(0.5)	3(0.5)	3(3.5)	6(1.1)
Bursitis	0(0.0)	1(0.2)	1(0.2)	2(2.3)	3(0.5)
Fungal infection	0(0.0)	1(0.2)	1(0.2)	2(2.3)	3(0.5)

* all patients received Ali/Aml 150/5 mg for 2 weeks, followed by Ali/Aml 300/10 mg for 52 weeks.
Preferred terms are sorted in descending frequency, as reported in the All Ai/Aml column.

In group D (controlled long term), the AE incidence was greater in the patients receiving add-on amlodipine and similar to HCT+amlodipine (63.3%, 49.9% and 62.0% in the aliskiren+amlodipine, aliskiren monotherapy and HCT+amlodipine groups, respectively). The AE incidence in the aliskiren+amlodipine and HCT+amlodipine groups was similar for peripheral oedema (10.9% vs 10.5%), headache (6.9% vs 7.5%) and fatigue (2.8% vs 2.3%), less for dizziness (1.2% vs 3.0%), cough (0.8% vs 3.0%) and diarrhoea (1.6% vs 3.0%) and greater for myalgia (2.4% vs 0.8%), eczema (4.0% vs 2.3%), hypercholesterolaemia (2.0% vs 0.4%) and palpitations (2.0% vs 0.0) (Table 19).

Table 19: Number (%) of patients with most frequent AEs (at least 2% for any treatment group) by preferred term, Group D

Preferred term	Mono Ali N=561 n (%)	All Ali/Aml N=248 n (%)	Ali total N=562 n (%)	Mono HCTZ N=544 n (%)	All HCTZ/Aml N=266 n (%)	HCTZ total N=544 n (%)
Any AE	280 (49.9)	157 (63.3)	357 (63.5)	266 (48.9)	165 (62.0)	337 (61.9)
Edema peripheral	4 (0.7)	27 (10.9)	30 (5.3)	6 (1.1)	28 (10.5)	31 (5.7)
Headache	21 (3.7)	17 (6.9)	37 (6.6)	33 (6.1)	20 (7.5)	52 (9.6)
Back pain	17 (3.0)	11 (4.4)	28 (5.0)	16 (2.9)	10 (3.8)	25 (4.6)
Nasopharyngitis	14 (2.5)	11 (4.4)	25 (4.4)	16 (2.9)	14 (5.3)	30 (5.5)
Eczema	10 (1.8)	10 (4.0)	19 (3.4)	6 (1.1)	6 (2.3)	12 (2.2)
Respiratory tract infection	3 (0.5)	8 (3.2)	11 (2.0)	3 (0.6)	4 (1.5)	6 (1.1)
Fatigue	12 (2.1)	7 (2.8)	18 (3.2)	10 (1.8)	6 (2.3)	15 (2.8)
Pharyngitis	10 (1.8)	7 (2.8)	17 (3.0)	8 (1.5)	4 (1.5)	12 (2.2)
Abdominal pain upper	5 (0.9)	6 (2.4)	11 (2.0)	6 (1.1)	6 (2.3)	12 (2.2)
Arthralgia	11 (2.0)	6 (2.4)	17 (3.0)	13 (2.4)	6 (2.3)	18 (3.3)
Bronchitis	16 (2.9)	6 (2.4)	21 (3.7)	15 (2.8)	3 (1.1)	18 (3.3)
Myalgia	7 (1.2)	6 (2.4)	13 (2.3)	8 (1.5)	2 (0.8)	10 (1.8)
Hypercholesterolemia	13 (2.3)	5 (2.0)	18 (3.2)	14 (2.6)	1 (0.4)	15 (2.8)
Palpitations	4 (0.7)	5 (2.0)	9 (1.6)	4 (0.7)	0 (0.0)	4 (0.7)
Pruritus	5 (0.9)	5 (2.0)	10 (1.8)	1 (0.2)	4 (1.5)	5 (0.9)
Skin papilloma	2 (0.4)	5 (2.0)	7 (1.2)	0 (0.0)	3 (1.1)	3 (0.6)
Vertigo	8 (1.4)	5 (2.0)	13 (2.3)	5 (0.9)	1 (0.4)	6 (1.1)
Diarrhea	12 (2.1)	4 (1.6)	16 (2.8)	8 (1.5)	8 (3.0)	16 (2.9)
Influenza	10 (1.8)	4 (1.6)	14 (2.5)	8 (1.5)	6 (2.3)	14 (2.6)
Dizziness	15 (2.7)	3 (1.2)	18 (3.2)	19 (3.5)	8 (3.0)	27 (5.0)
Gastroenteritis	8 (1.4)	3 (1.2)	11 (2.0)	2 (0.4)	2 (0.8)	4 (0.7)
Musculoskeletal pain	4 (0.7)	3 (1.2)	6 (1.1)	9 (1.7)	2 (0.8)	11 (2.0)
Cough	14 (2.5)	2 (0.8)	16 (2.8)	14 (2.6)	8 (3.0)	22 (4.0)
Dyspepsia	9 (1.6)	2 (0.8)	11 (2.0)	4 (0.7)	2 (0.8)	6 (1.1)
Tendonitis	4 (0.7)	2 (0.8)	6 (1.1)	4 (0.7)	6 (2.3)	9 (1.7)
Hypertriglyceridaemia	11 (2.0)	1 (0.4)	12 (2.1)	5 (0.9)	2 (0.8)	7 (1.3)

Preferred terms are sorted in descending frequency, as reported in the All Ai/Aml column.

Adverse events that were most likely to be assessed as drug related by the investigator included peripheral oedema, headache and dizziness. AE intensity was generally mild or moderate with 1.0% of AEs judged as severe in aliskiren/amlodipine patients compared to 0.2%, 0.8% and 0.5% of the respective monotherapies and placebo groups in group B. Peripheral oedema was only severe in one aliskiren/amlodipine patient (150/10 mg) in group B. In group C, severe AEs were reported in 8.1% of patients overall and 7.2% of patient on aliskiren/amlodipine alone with severe peripheral oedema and severe diarrhoea occurring in 1.3% and 0.4%, respectively. In group D severe AEs occurred in 2.0% of the aliskiren+amlodipine group compared to 1.4% of aliskiren monotherapy and 4.9% of the HCT+amlodipine group.

Serious Adverse Events and Deaths

Deaths

There were no deaths reported in any of the clinical trials evaluated. To the cut-off of 31 July 2009, there have been 2 deaths in an ongoing trial (SAH100A2302) which occurred during the placebo run-in period; one due to “unknown street drug” and the other from an unknown cause.

SAEs

The SAE rate was generally low. In group A and B, SAEs occurred in 0.7% (5/724) and 0.9% (19/2031) of aliskiren/amlodipine treated subjects, respectively compared to 1.0% of placebo treated subjects. The most frequent SOC was *Infections and Infestations* (0.2%). In group B, SAEs that led to study discontinuation in the aliskiren/amlodipine groups were cerebrovascular accident, diabetic hyperglycaemic coma, diverticulitis and lobar pneumonia. There were two other SAE related discontinuations, myocardial infarction and abdominal mass, in the amlodipine and placebo groups, respectively.

In group C, the SAE rate was 2.7% with 4 SAEs leading to discontinuation (atrial fibrillation, metastatic prostate cancer, depression with attempted suicide and hypotension). In group D, the SAE rate was 4.8% and 4.5% in the aliskiren+amlodipine and HCT+amlodipine groups, respectively with neoplasms being the most frequent SAE (1.6% vs 0.8%). There was one patient who discontinued aliskiren/amlodipine due to an SAE (breast cancer). In the pharmacology studies, there was one SAE of cellulitis.

Laboratory findings and vital signs

There were no notable changes in liver function tests (LFTs) in the studies nor any meaningful change in lipids in group A. Urinalysis was not done in the studies and electrocardiograms (ECGs) were performed at baseline only.

Haematology

The mean change from baseline in haemoglobin for the all aliskiren/amlodipine treated patients was -1.8 g/L in group A and -2.0 g/L in Group B studies compared to 1.4 g/L for the placebo group. There were 4 (0.2%) aliskiren/amlodipine patients with a >20% decrease in haemoglobin (group B), 2 patients remained within the normal range and 2 were below normal. In group C, the mean decrease in haemoglobin was -1.9g/L. The decrease was less in group D, -0.1 g/L for aliskiren+amlodipine compared to 2.8 g/L in those treated with HCT+amlodipine. There were 1.2% of aliskiren+amlodipine patients in group D who had a >20% decrease in haemoglobin.

Clinical chemistry

In group A, there was a slight increase from baseline to study end in the mean (0.055 to 0.073 mmol/L) and median (0.100 mmol/L) serum potassium in the aliskiren/amlodipine combination therapy groups, which was not more than that seen in the aliskiren monotherapy group (mean of 0.065 to 0.117 mmol/L and median of 0 to 0.1 mmol/L). In group B, the number of patients with serum potassium >5.5 mmol/L at any post baseline visit was low: 1.0%, 0.6%, 0.7% and 0.5% of the aliskiren/amlodipine, aliskiren, amlodipine and placebo groups, respectively. In group D, serum potassium >5.5 mmol/L occurred at a higher rate in the aliskiren and aliskiren+amlodipine groups (6.3% and 6.9%) compared to the HCT and HCT+amlodipine groups (3.8% in both). Potassium ≥6 mmol/L occurred in 2.8% of the aliskiren+amlodipine compared to 1.5% of the HCT+amlodipine treated subjects.

In group B, an increase of blood urea nitrogen >14.28 mmol/L at any visit occurred in 0.2% and 0% of the aliskiren/amlodipine and monotherapy groups, respectively, compared to 0.5% of the placebo group. An increase in serum creatinine >176.8 µmol/L occurred in one subject (<0.1%) in the aliskiren/amlodipine groups and none in other groups.

Vital signs

There were no relevant changes in body weight or pulse rate in the safety groups. Orthostatic hypotension was defined as a decrease in SBP of at least 20 mmHg or DBP of at

least 10 mmHg on moving from sitting to standing. In group A, the orthostatic hypotension rate at any individual visit ranged from 0.0% to 4.0% in patients treated with aliskiren/amlodipine (any dose). The incidence at any post baseline visit was 8.1%, 8.3%, 5.4% and 10.1% in the all aliskiren/amlodipine, amlodipine, aliskiren and placebo groups, respectively. Similar results were found in group B. In the long term open label study (group C), the overall incidence of orthostatic hypotension at any visit was 8.6% in aliskiren/amlodipine treated patients and rose to 14.0% when HCT was added. From group D, the incidence was slightly higher with combination treatment (15.0% aliskiren+amlodipine) than aliskiren monotherapy (9.2%) or HCT+amlodipine (12.0%). The incidence at any single visit ranged from 1.6% to 3.8% in subjects treated with aliskiren+amlodipine.

Safety in special populations

Age

Safety data was assessed by age groups of ≥65 years and ≥75 years. In group B, in subjects treated with aliskiren/amlodipine, the AE incidence in those aged ≥65 years (n=105) was slightly lower than those aged <65 years (29.8% vs 33.5%). The rate was 29.8% in those aged ≥75 years, though this was based on only 15 patients. There was a similar discontinuation rate due to AEs in those aged <65 years and ≥65 years treated with aliskiren/amlodipine (2.5% vs 2.3%). AEs possibly related to hypotension were reviewed and there was no increase in the elderly. In the long term studies, there was no increase in AEs in the elderly (≥65 years) except for a slightly higher rate of dizziness (6.9% vs 4.6% in group C).

Gender

The rate of peripheral oedema was higher in women than men (7.6% vs 4.5% in group B). There were no other notable differences in safety findings by gender.

Race

There were not evident differences in AE frequency or nature in Black (n=431) or Asian patients (n=395) in group B. There were too few non-Caucasians in the long term studies to draw conclusions.

Renal function

AEs and laboratory values were examined for patients with mild (estimated glomerular filtration rate [eGFR] 60-90 mL/min/1.73m^2) and moderate renal impairment (eGFR 30-60 mL/min/1.73m^2) and compared to those with normal renal function (eGFR ≥90 mL/min/1.73m^2). In group B, 4% (171/3890) of the population had moderate renal impairment and there were no evident differences in AE frequency or nature. There was one AE of renal failure and one of renal impairment in patients with moderate renal impairment treated with aliskiren/amlodipine 150/5 mg and 150/10 mg, respectively. In group C, 4% had moderate renal failure and there was one case of acute renal failure with diarrhoea and volume depletion. In group D the nature and frequency of AEs was similar between those with renal impairment and normal renal function.

Diabetes

AE incidence was not notably different in diabetics compared to non-diabetics treated with aliskiren/amlodipine (36.4% vs 32.4% in group B and 56.7% vs 64.2% in group D). There were no evident differences in AE nature in diabetics.

Obesity

Nearly half the population studied were obese (BMI ≥30 kg/m^2) and AE frequency was similar to non-obese.

Stage 2 hypertension

Stage 2 hypertension was defined as msSBP ≥160 mmHg and msDBP ≥100 mmHg. The incidence of AEs was similar to the overall population in the short term and long term studies.

Discontinuation due to Adverse Events

In group B short term studies, discontinuation due to safety reasons[16] occurred in 2.5% of all subjects, with the highest rate in the monotherapy amlodipine group (3.6%) compared to 1.2% of monotherapy aliskiren, 2.5% of aliskiren/amlodipine and 2.0% of the placebo group. In group C (long term, open label study), discontinuation due to safety reasons occurred in 12.8% and 8.1% of the aliskiren/amlodipine and aliskiren/amlodipine+HCT groups, respectively. In group D (long term, controlled study), safety related discontinuation was highest in subjects receiving HCT (7.2%) and HCT+amlodipine (7.2%) compared to 5.8% with aliskiren monotherapy (5.8%) and aliskiren+amlodipine (4.0%). Peripheral oedema was the most common AE leading to discontinuation of aliskiren/amlodipine treated patients (0.7% in group B, 6.5% group C, and 0.4% in group D).

Post marketing experience

The submission stated that the combination product has not yet been marketed in any country up to its compilation date of October 2009. The sponsor estimated an exposure to aliskiren of approximately 460,000 patient treatment years (PTY). Since the start of marketing in 1997, the total exposure to amlodipine (monotherapy and combination therapies) is approximately 325 million PTY. There were 320 cases (1268 events) on the sponsor's database of reported events with concurrent use of aliskiren and amlodipine, with the most common serious cases being increased creatinine, peripheral oedema, angioedema, dyspnoea, hypertension, BP increased, fatigue and headache.

Evaluator's overall conclusions on clinical safety

Safety data were collected from 5549 patients with 2835 who received at least one dose of aliskiren/amlodipine combination, 612 of whom were exposed for 6 months and 372 for 12 months. The median exposure was 56 days in the short term, placebo controlled study.

The overall incidence, as well as that of individual AEs, was found to be similar to component monotherapies and AEs were not noted to be dose dependent. The exception to this was peripheral oedema which was the most frequent AE and appeared related to the 10 mg amlodipine dose; rates of 13.6%, 13.8% and 1.1% in the aliskiren/amlodipine 300/10 mg, monotherapy amlodipine 10 mg and aliskiren/amlodipine 300/5 mg groups, respectively, were seen in the short term studies. In the open label, long term study of aliskiren/amlodipine 300/10 mg, peripheral oedema occurred in 22.7% of patients. Peripheral oedema was found to be more frequent in women compared to men treated with aliskiren/amlodipine (7.6% vs 4.5% in group B) and was the AE most frequently leading to discontinuation of aliskiren/amlodipine treatment (0.7% in short term studies and 6.5% in long term open label study).

Other AEs such as headache, diarrhoea, cough, dizziness were not more frequent in the combination compared to monotherapy groups in the short term studies. There was a

[16] "Safety reasons" included AEs, death, abnormal laboratory value or abnormal test procedure result

similar AE incidence in patients treated with aliskiren+amlodipine and HCT+amlodipine (63.3% vs 62.0%) in the long term controlled study.

In general, AEs in patients treated with aliskiren and amlodipine were mild to moderate in severity with only 1.0% of AEs in the short term studies and 2.0% of AEs in the long term controlled study being assessed as severe, although in the long term open label study the rate of severe AEs rose to 8.1%. There were 2 cases of severe diarrhoea (0.4%) in the long term open label study. There were no deaths in the clinical trials evaluated, though there were 2 in ongoing studies in subjects not exposed to active treatment. The SAE rate was 0.9% in the aliskiren/amlodipine groups in the short term studies (1.0% in placebo group) and 4.8% and 4.5% in the aliskiren+amlodipine and HCT+amlodipine groups, respectively, in the long term controlled study.

On laboratory assessment, there was a small mean decrease in haemoglobin (-2.0 g/L in short term studies) with 1.2% of aliskiren+amlodipine subjects in the long term controlled study having a >20% decreased in haemoglobin. There was a small increase (median 0.1 mmol/L) in serum potassium that was similar to aliskiren monotherapy in the short term placebo controlled study and with longer term treatment the proportion of patients with a serum potassium >5.5 mmol/L at any visit was similar between the aliskiren+amlodipine and HCT+amlodipine groups (6.3% vs 6.9%). There were no other notable findings on laboratory assessments.

In the long term controlled study, orthostatic hypotension at any one visit was slightly more common in aliskiren+amlodipine subjects (15.0%) compared to aliskiren monotherapy (9.2%) and HCT+amlodipine subjects (12.0%), although the incidence at a single visit was low and ranged from 1.6% to 3.8%.

A subgroup analysis (age, race, obesity, diabetes, Stage 2 hypertension and renal impairment) did not show any notable safety findings and reflected safety results in the overall population. Discontinuation of the combination therapy was not higher than monotherapy and was less than HCT+amlodipine treatment. From post marketing data, the most common severe cases reported with concurrent use of aliskiren and amlodipine were increased creatinine, peripheral oedema, angioedema, dyspnoea, hypertension, BP increased, fatigue and headache.

The effect of treatment withdrawal (such as rebound hypertension) was not assessed in the clinical program, though it is noted that no effects are noted on the product information for either monotherapy.

The safety of aliskiren/amlodipine has not been assessed in patients with more severe degrees of hypertension nor in pregnancy. There were two pregnancies in the clinical program, one was terminated and the outcome of the second was unknown. As drugs acting on the renal angiotensin system have known fetal and neonatal risks, aliskiren/amlodipine should not be used in pregnancy.

Overall, the aliskiren/amlodipine combination appeared well tolerated with a safety profile similar to the component monotherapies and no new safety signals were evident from the data submitted.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Pharmacokinetics

Can the sponsor verify that the selected variant (Study SPA100A22101) was the formulation used in studies SPA100A22102 to SPA100A22104**.** Can the sponsor justify why they have not demonstrated the bioequivalence of the 150/05 mg and 300/05 mg fixed combination tablets with the corresponding doses of the individual drugs?

Efficacy

In the short term clinical trials (SPA2305, SPA2303, SPA2304 and SPP2305) there were no rates of treatment compliance reported in the clinical study reports, yet it was stated the monitors checked compliance at monitoring visits. Please provide the details of treatment compliance from these studies together with comments on the rates?

The submission refers to ongoing clinical trials in moderate to severe hypertension. Are the data on the efficacy of aliskiren/amlodipine combination in patients with moderate to severe hypertension available? If so, please submit these data. Is there relevant information from these studies that should be included on the product information/Consumer Medicines Information (CMI)?

Safety

Are the data on the safety of aliskiren/amlodipine combination in patients with moderate to severe hypertension available? If so, please submit these data. Is there relevant information from these studies that should be included on the product information/CMI?

Longer term GI toxicity studies were to be submitted in relation to aliskiren. Please comment on these data, if available, and if any relevant details need inclusion in the aliskiren/amlodipine product information?

There were also a number of questions relating to the PI and the CMI but these are beyond the scope of this AusPAR.

Clinical Summary and Conclusions

Clinical Aspects

Pharmacokinetics

The studies demonstrated that the aliskiren/amlodipine fixed combination tablet at doses of 300/10 mg and 150/10 mg were bioequivalent with the corresponding doses of the free combination aliskiren/amlodipine tablets. In addition, the sponsor demonstrated that when the fixed combination SPA100 (aliskiren/amlodipine 300/10 mg oral tablets) is given following a high-fat breakfast the C_{max} and AUC_{inf} of aliskiren are reduced by approximately 90% and approximately 80%, respectively, compared to fasted conditions. By contrast, food had little effect of the pharmacokinetics of amlodipine.

The sponsor has only demonstrated the bioequivalence of the 300/10 mg and the 150/10 mg doses of the fixed combination tablets with the corresponding doses of the individual drug. No information has been provided regarding the bioequivalence of the other proposed dosage strengths (150/5 mg and 300/5 mg) that are contained in the application.

Clinical Efficacy

Overall, the combination of aliskiren/amlodipine, at doses of 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg, resulted in a consistent and clinically meaningful reduction in DBP and SBP with compared to placebo and respective monotherapies, with the exception that aliskiren/amlodipine 150/10 mg and 300/10 mg were found to be no better than monotherapy amlodipine 10 mg in SBP reduction. There was a dose response with greater

BP reduction with the higher dose combinations. The placebo subtracted mean reductions in DBP and SBP from the pivotal trial are presented in Table 8.

The aliskiren/amlodipine combinations also resulted in statistically significant improvement in BP control (<140/90 mmHg) rates compared to the respective monotherapy components, with the highest rate of 68.3% with the highest dose combination aliskiren/amlodipine 300/10 mg. This rate was greater than for amlodipine 10 mg monotherapy (50.3%) despite no greater reduction in mean SBP.

There were 352 aliskiren/amlodipine patients in the placebo controlled study who had 24 hour ABPM. Efficacy was confirmed on MABP with statistically significant and clinically meaningful reductions in MADBP and MASBP compared to component monotherapies. Mean hourly BP showed sustained reduction over the 24 h period with once daily dosing.

Efficacy in terms of mean SBP and DBP reduction as well as BP control rates was seen in patients not adequately responsive to aliskiren monotherapy (300 mg) or amlodipine monotherapy (10 mg and 5 mg) in the 3 active controlled trials. In subjects not responding to aliskiren 300 mg, the statistically significant difference, compared to aliskiren monotherapy, in the BP change from baseline was -11.62/-7.23 mmHg for aliskiren/amlodipine 300/10 mg and -8.01/-4.71 for the 300/5 mg combination.

For those not responding to 10 mg amlodipine, the improvement compared to monotherapy was greater with aliskiren/amlodipine 300/10 mg (-6.22/-3.76 mmHg) compared to 150/10 mg (-2.81/-1.72 mmHg) though both were statistically significant. For patients not responding to amlodipine 5 mg, aliskiren 150 mg + amlodipine 5 mg resulted in a statistically significant reduction in BP compared to amlodipine 5 mg (-6.02/-3.62 mmHg), however this was not significantly greater than that achieved with amlodipine 10 mg monotherapy (-1.35/-0.42 mmHg).

The efficacy of aliskiren/amlodipine was seen across subgroups (age, gender, diabetes, renal impairment), although there were too few Blacks in the placebo controlled study to draw meaningful conclusions in this group. In addition, there were low numbers of subjects aged over 75 years in the development program. The antihypertensive effect was seen after 2 weeks treatment and maximal effect was maintained throughout the studies' duration of up to 54 weeks with no evidence of tolerance. Rebound hypertension on treatment withdrawal was not assessed.

Clinical Safety

Safety data were presented from the 7 short term and long term studies in which 2835 patients received at least 1 dose of aliskiren/amlodipine combination, 612 received it for at least 6 months and 372 for 1 year. These numbers are within guideline recommendations. The mean age of patients was 54 to 57 years with low numbers of those aged ≥75 years (2-4%) as mentioned above. Approximately half of the study population were women, were obese (BMI ≥30 kg/m^2) and had predominantly mild renal impairment (eGFR <90 mL/min/1.73m^2). Between 11 and 16% of all the study population had diabetes. This population appears representative of the target hypertensive population in Australia.

The aliskiren/amlodipine combination was found to be well tolerated with the overall incidence, as well as that of individual AEs, similar to component monotherapies and AEs were not dose dependent. The exception to this was peripheral oedema which was the most frequent AE and occurred in 13.6%, 13.8% and 1.1% of the aliskiren/amlodipine 300/10 mg, monotherapy amlodipine 10 mg and aliskiren/amlodipine 300/5 mg groups, respectively in the short term studies. Peripheral oedema is a known adverse reaction with amlodipine and in the studies this AE appeared related to the 10 mg amlodipine dose.

Other AEs, such as headache, diarrhoea, cough and dizziness were not more frequent in the combination compared to monotherapy groups in the short term studies. The long term studies found a similar pattern of AEs with no additional signals.

The severity of AEs were generally mild to moderate with only 1% of AEs assessed as severe in the short term studies, although this rose to 8% in the long term open label study. There were no deaths in the clinical trials reported and the SAE rate was 0.9% in the aliskiren/amlodipine groups (1.0% placebo group) in the short term studies and 4.8% and 4.5% in the aliskiren+amlodipine and HCT+amlodipine groups, respectively in the long term controlled study and 2.7% in the long term open label study which assessed the highest dose. There was no evident pattern in the SAEs observed.

As with aliskiren monotherapy, a small decrease in mean haemoglobin was seen (-2.0g/L in short term studies) and a small increase in serum potassium (median 0.1 mmol/L in short term studies) was seen. Potassium >5.5 mmol/L at any visit was similar between the aliskiren+amlodipine and HCT+amlodipine groups (6.3% vs 6.9%) in the long term controlled study. There were no other notable findings on laboratory assessments.

The incidence of orthostatic hypertension at a single visit was low (1.6% to 3.8% in long term controlled study) and overall the incidence was only marginally higher with aliskiren/amlodipine (all doses) than amlodipine 10 mg (7.6% vs 6.6% in the short term studies).

There were no notable safety findings across the subgroups of gender, age, race, renal function or diabetes. Study discontinuation due to safety reasons was low in patients treated with aliskiren/amlodipine (2.5% compared to 2.0% in placebo group) in the short term controlled studies. With longer treatment, discontinuation due to AEs rose and occurred in 12.1% of patients in the long term open label study of the highest dose combination. Peripheral oedema was the main AE leading to discontinuation.

Benefit risk assessment

Benefits

The aliskiren/amlodipine combination tablet includes one drug, aliskiren that is the first in its class and the other, amlodipine, which is well known and currently widely used. The clinical program was thorough and designed in accordance with relevant guidelines.

All the aliskiren/amlodipine combination doses resulted in clinically meaningful and statistically significant antihypertensive effect together with greater BP control rates than the respective monotherapies. Both components of the combination were found to contribute to the reduction in BP. There was an evident dose response with higher BP reduction at higher combination doses. The antihypertensive effect was maintained over 24 h on ABPM, was seen within 2 weeks and was sustained over 1 year of treatment with no evidence of tolerance. Efficacy was seen across subgroups.

Aliskiren/amlodipine had an acceptable safety profile similar to the component monotherapies and there were no new safety signals with the combination therapy.

The treatment is a once a day dosing of a single tablet which may assist in patient compliance.

While aliskiren/amlodipine 150/5 mg was found to be no better than 10 mg amlodipine at lowering BP, it did result in a lower rate of peripheral oedema which may be a use for patients not tolerating the 10 mg amlodipine dose.

Risks

The main risk of aliskiren/amlodipine treatment is peripheral oedema with combinations containing 10 mg amlodipine. This is a known effect with amlodipine and did not occur at a greater rate than the monotherapy amlodipine 10 mg. In the long term open label study of aliskiren/amlodipine 300/10 mg, the discontinuation rate due to AEs rose to 12.1% indicating a degree of intolerance of this dose with longer term treatment. The other AEs seen were in line with monotherapies though there was no increase in diarrhoea that has been noted with aliskiren monotherapy.

Aliskiren/amlodipine combination resulted in a small decrease in haemoglobin, as seen with aliskiren that was not clinically significant. In addition, there was also a small increase in serum potassium that again was not greater than seen with aliskiren monotherapy. Orthostatic hypotension did occur, though the rate was relatively low and the incidence of dizziness was not greater than monotherapy.

As reported in postmarketing data for aliskiren monotherapy, there could potentially be risks of angioedema and acute renal failure with the combination therapy.

Rebound hypertension was not assessed, though it is not anticipated to be an issue as withdrawal effects are not mentioned in the respective monotherapy PIs.

Subgroup analysis found too few Blacks and patients aged over 75 years for meaningful conclusions to be made. There is a lack of efficacy and safety data in patients with moderate to severe hypertension, secondary hypertension, as well as patients with severe hepatic and renal impairment, cardiovascular or cerebrovascular disorders. There are no data in pregnancy.

Information on the monotherapies notes numerous drug interactions and these will obviously continue to add to the risk profile of the combination treatment.

There are currently no morbidity or mortality outcome data available for aliskiren, though it is noted a clinical trial assessing this is in progress.

Balance

It is well established that lower blood pressure is associated with a lower risk of stroke, coronary heart disease, chronic renal disease and heart failure and so the active management of hypertension is an important part of health care in Australia. When antihypertensive medication is required, Australian guidelines recommend commencing with the lowest dose of a first line agent. A second agent, from a different class, is only added if the target BP is not reached or there is no significant reduction with the initial monotherapy (Heart Foundation, 2010).[17] It is reported that between 50 and 75% of patients with hypertension will not achieve their target BP with monotherapy (Hansson 1998) and in this group combination antihypertensive therapy has a clinical place.[18]

An indication for aliskiren/amlodipine combination covering first line treatment of hypertension has been sought in other countries. However, in Australia, in line with the decision in relation to the aliskiren/hydrochlorothiazide combination and the current treatment guidelines, initial therapy indication was not requested by the sponsor for aliskiren/amlodipine. Therefore, the risk benefit assessment was only undertaken for replacement therapy and for add-on therapy in those poorly responding to a component monotherapy.

[17] Heart Foundation (2010). Guide to management of hypertension 2008. Updated 2010.

[18] Hansson L, Zanchetti A, Carruthers SG et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998; 351: 1755–1762.

The doses in the combination tablets are the same as the registered monotherapy doses and pharmacokinetic and pharmacodynamic data have shown equivalence between the separate tablets and the combination tablets across the dose range. These data, together with the positive clinical efficacy and acceptable safety data, allowed the evaluator to conclude that the aliskiren/amlodipine combination tablet is an appropriate replacement therapy for the concurrent use of separate tablets.

The data from the 3 short term add-on studies support the additional BP lowering efficacy of the aliskiren/amlodipine combination in patients not adequately responding to aliskiren or amlodipine monotherapy. This is supported by data from the placebo controlled short term study and the longer term studies. The safety profile of the combination did not show evidence of deterioration, nor any new safety signals, in comparison to the monotherapies. These factors led the evaluator to conclude that aliskiren/amlodipine combination was an appropriate antihypertensive treatment option for patients requiring an additional therapeutic agent.

There was a lack of data on the elderly (≥75 years) and the trials did not include a number of patients groups (severe hypertension, secondary hypertension, severe hepatic or renal impairment, cardiovascular or cerebrovascular disorders and pregnancy) and this needs to be adequately addressed in the PI. Data coming from areas of further study of the combination therapy (such as study SPA2306 in moderate to severe hypertension)[19] as well as with aliskiren monotherapy (such as renal failure, gastrointestinal toxicity and the clinical outcome study) need to be provided in a timely fashion for assessment to ensure there is no change to the risk benefit balance and so that the product information can be updated accordingly.

In summary, the evaluator found the risk-benefit balance in favour of second line indications in the treatment of primary hypertension, that is, in patients whose BP is inadequately controlled on aliskiren or amlodipine monotherapy and for replacement therapy in patients who are already being treated with aliskiren and amlodipine concurrently at the same dose level as the combination.

Conclusions

It was concluded that the overall benefit risk balance of aliskiren/amlodipine combination tablet was positive for the indication of

Rasilamlo is indicated for the treatment of hypertension. Treatment should not be initiated with these fixed dose combinations.

It was recommended that registration should be conditional on the sponsor supplying, when available, the additional safety and efficacy data of aliskiren/amlodipine combination therapy in patients with moderate to severe hypertension together with data that has been requested in relation to aliskiren monotherapy registration.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

[19] SPA2306 is a double blind, 8 week, efficacy and safety study of aliskiren/amlodipine in 484 patients with moderate to severe hypertension.

Safety Specification

The sponsor indicated that the important identified and potential risks of the fixed combination aliskiren/amlodipine product are expected to be similar to those reported in the aliskiren RMP and those identified for amlodipine and described in the CCDS for aliskiren/amlodipine.[20]

Aliskiren

The summary of the ongoing safety concerns in relation to aliskiren, used alone or in combination with other anti-hypertensive agents in the hypertensive population, as specified by the sponsor, are shown in Table 20.

Table 20: Ongoing safety concerns for aliskiren

Important identified risks	Diarrhea Rash Angioedema Hyperkalemia Decreases in hemoglobin and hematocrit Renal dysfunction
Important potential risks	Colorectal hyperplasia Peripheral edema Hypotension
Important identified interactions	Increased aliskiren systemic levels with the potent Pgp inhibitor, ciclosporin Decrease in furosemide systemic levels
Important potential interactions	Increased aliskiren systemic levels with other moderate (itraconazole, clarithromycin, telithromycin, erythromycin, amiodarone) and potent Pgp inhibitors (quinidine) Increased aliskiren systemic levels with grapefruit juice
Pharmacological class effects	Cough
Pharmacological class interactions	NSAIDs: increase in BP and renal function deterioration.
Important missing information	Pregnancy Pediatric patients Severe and moderate renal dysfunction Reno-vascular hypertension Benefit on cardiovascular morbidity and mortality Drug-drug interaction with grapefruit juice

Amlodipine

The summary of the ongoing safety concerns for amlodipine as specified by the sponsor are shown in Table 21.

[20] A Company Core Data Sheet (CCDS) is a company-internal global reference labelling document used to direct the content of local (affiliate) labelling.

Table 21: Ongoing safety concerns for amlodipine

System organ class	Reported ADRs
Cardiovascular	arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), vasculitis, syncope, hypotension
Central and Peripheral Nervous System	neuropathy peripheral, tremor, dizziness, dysgeusia, headache, paraesthesia, somnolence
Gastrointestinal & hepatobiliary	gastritis, gingival hyperplasia, pancreatitis, altered bowel habit, hepatic enzyme elevation, hepatitis, dyspepsia, nausea/vomiting, abdominal pain upper, diarrhea, dry mouth
General	malaise, weight gain, weight loss, hypersensitivity, asthenia, non-cardiac chest pain
Hemopoietic	leukopenia, thrombocytopenia
Musculoskeletal System	arthralgia, myalgia, muscle spasm
Psychiatric	mood changes, insomnia
Respiratory System	rhinitis, dyspnea, cough
Skin and Appendages	alopecia, angioedema, rash, erythema multiforme, purpura, skin discoloration, urticaria, hyperhidrosis, pruritus
Special Senses	tinnitus, visual disturbance
Urinary System	increased urinary frequency, nocturia, micturition disorder, pollakiuria
Metabolic and Nutritional	hyperglycemia
Reproductive system	impotence, gynaecomastia

The OPR reviewer noted that details of important identified and potential risks for aliskiren, such as seriousness/outcomes, frequency, preventability and potential public health impact, are provided in the aliskiren RMP but this information is not included in the RMP for aliskiren/amlodipine. The basis for including the adverse effects described in the CCDS for amlodipine as ongoing safety concerns is not stated in the RMP.

Adverse events anticipated by the sponsor with aliskiren, based on their association with other drugs that act on the renin-angiotensin system, include hyperkalaemia, decreases in haemoglobin and haematocrit, angioedema, cough and changes in renal function. The potential interaction of aliskiren and NSAIDs has also been identified as an issue. This potential interaction and the anticipated adverse events are included in the ongoing safety concerns.

Amlodipine is a dihydropyridine calcium channel blocker. Class effects of calcium channel blockers include flushing, headache, dependent oedema, nausea and dizziness.[21] Only nausea and dizziness are specified as ongoing safety concerns by the sponsor.

Nonclinical comments on the RMP Safety Specification

The nonclinical evaluator noted that all potential clinically relevant toxicological findings have been adequately identified and described in the RMP.

Clinical comments on the RMP Safety Specification

The clinical evaluator noted that the sponsor stated that due to the bioequivalence of the fixed combination to the free combinations of the monotherapies and that no additional

[21] Wing, LMH. Calcium channel antagonists. Australian Prescriber [serial online]. 1997; 20:5-8. Accessed 17 August 2010. Available from: http://www.australianprescriber.com/magazine/20/1/5/8/#top.

risks for the combination have been identified, the risks are considered the same as those for the use of aliskiren and amlodipine alone. Therefore, the sponsor plans to apply the same pharmacovigilance activities for the fixed combination as the monotherapies and the RMP plan has no additional risks included for monitoring. The evaluator has not noted any additional risks for inclusion in the RMP though recommends that the RMP should include studies with the combination product as well as those with aliskiren.

Pharmacovigilance Activities

Routine and additional pharmacovigilance activities were proposed in relation to safety concerns identified for aliskiren and routine pharmacovigilance activities were proposed in relation to safety concerns identified for amlodipine.[22]

The OPR reviewer noted that the aliskiren RMP contains a detailed action plan for each safety concern including the actions proposed, the objective and rationale of the proposed actions, further actions that may be adopted on the basis of the results of the action and milestones for evaluation and reporting. This information was not, however, included in the RMP for aliskiren/amlodipine. With regard to amlodipine, a detailed action plan in relation to the safety concerns was not included in the RMP.

The OPR reviewer further noted that it was anticipated that reports of adverse effects associated with drug abuse or misuse, off-label use and paediatric off-label use will be reported in PSURs for aliskiren/amlodipine. This seemed adequate at this point in time. It was also anticipated that adverse effects associated with use of aliskiren/amlodipine beyond the duration of the clinical trials will be reported in PSURs for aliskiren/amlodipine.

Additional pharmacovigilance activities in relation to ongoing safety concerns for aliskiren include studies and targeted follow up using questionnaires /checklists. It was indicated that questionnaires/checklists will be used to collect information in relation to diarrhoea, angioedema, colorectal hyperplasia and pregnancy. These questionnaires do not appear to be provided with the RMP.

Based on the study protocol overview in the aliskiren/amlodipine RMP, it was anticipated that the submission of final data has occurred for three of the studies addressing safety concerns in relation to aliskiren, studies SPP100A2112, 1939-017 and SPP100A2404, and that the final study reports would be available for review. The start of enrolment for study SPP100A2255 was planned for March 2010. Paediatric studies for aliskiren are planned. Study protocols do not appear to have been provided with the RMP.

The aliskiren RMP (version 5) indicates that an additional preclinical study (P0900355) was being undertaken to evaluate the mechanism of the increased aliskiren systemic levels with cyclosporin A. It appears that the final study report was due in late 2009. This study was not mentioned in the aliskiren/amlodipine RMP.

Study SP100A2340E1, included in the study protocol overview for the pharmacovigilance plan in the aliskiren RMP, was not referred to in the aliskiren/amlodipine RMP. The study

[22] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

title did not appear to be provided in the aliskiren RMP. The planned date for submission of final data is August 2012.

Risk Minimisation Activities

The sponsor stated that no additional safety risk was identified in the clinical trial program for amlodipine in combination with aliskiren and, therefore, no risk minimisation activities beyond routine risk minimisation activities are planned.[23] The sponsor also indicated that risk minimisation activities for the aliskiren/amlodipine fixed combination product will follow the approved plan for aliskiren monotherapy, detailed in the aliskiren RMP, and the existing labelling for amlodipine.

Based on the information provided in the RMP, the OPR reviewer agreed that routine risk minimisation activities appeared to be adequate. As amlodipine has been marketed for many years it seems reasonable to accept the sponsor's statement in the Safety Specification that the safety profile has been well defined and is adequately described in available prescribing information.

Conclusion

The OPR reviewer recommended to the Delegate that the sponsor be requested to:

- justify why, of the populations not studied in the pre-authorisation phase, only pregnancy is included in the proposed PI as a contraindication and, for the other populations not studied in the pre-authorisation phase, why a precautionary statement is included in the proposed PI for only some of the populations not studied
- provide comment on the implications for the safety of use of aliskiren/amlodipine in Australia with regard to the populations not studied or who had limited exposure in the SPA100 fixed combination development program
- provide the revised RMP for aliskiren/amlodipine, if it has been updated as proposed in PSUR 5 for aliskiren, and also the revised RMP for aliskiren and the latest CCDS for aliskiren and aliskiren/amlodipine
- add ventricular arrhythmias, hypertensive crises and cases of severe hyponatraemia as ongoing safety concerns to the RMP or justify why they should not be added
- specify in the aliskiren/amlodipine RMP, as per the aliskiren RMP, the details of important identified and potential risks for aliskiren in terms of seriousness/outcomes, frequency, potential mechanisms, preventability, public health impact and regulatory action taken and include such detail for the safety concerns identified for amlodipine also
- include in the RMP for aliskiren/amlodipine, an action plan for each safety concern identified for both aliskiren and amlodipine
- provide the questionnaires and checklists used in the targeted follow-up of safety concerns in relation to aliskiren, specifically diarrhoea, angioedema, colorectal hyperplasia and pregnancy
- for the safety concerns for aliskiren, severe renal dysfunction, reno-vascular hypertension, and cardiovascular morbidity and mortality reduction, clarify why the presentation of an aggregate analysis of available data in PSURs is included in the

[23] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

planned pharmacovigilance actions in the RMP for aliskiren but not in the corresponding table in the RMP for aliskiren/amlodipine

- provide the outcomes of studies SPP 100A2112, 1939-017 and SPP100A2404 and advise how the results will be incorporated into the RMP
- clarify the status of study P0900355, provide a summary of the outcome of this report if available, and advise how the results will be incorporated into the RMP
- provide further details regarding study SP100A2340E1
- provide the study reports for study SPP100A2255 and SPP100E2337 when available
- provide further information on the planned paediatric studies
- clarify why there are additional adverse reactions described in the Tekturna label that are not listed for aliskiren in the proposed aliskiren/amlodipine PI
- provide the study report for the clinical drug interaction study (SPP 100A2112) exploring the interaction between aliskiren and grape fruit juice, if available, and advise how the results will be incorporated into the RMP. If the study report is not yet available justify why the following statement has not been included in the proposed PI for aliskiren/amlodipine: "Due to lack of data a potential interaction between grapefruit juice and aliskiren cannot be excluded. Grapefruit juice should not be taken with Rasilez."
- provide the study report for studies 1939-017 and SP100A2404 addressing the potential risk of colorectal hyperplasia and advise how the results will be incorporated into the RMP
- clarify the status of the preclinical study (P0900355) undertaken to evaluate the mechanism of the increased aliskiren systemic levels with cyclosporin A and provide the study report if available, and advise how the results will be incorporated into the RMP
- provide details regarding study SP100A2340E1, included in the study protocol overview for the pharmacovigilance plan in the aliskiren RMP but not referred to in the aliskiren/amlodipine RMP.

The reviewer also made a number of comments with respect to the PI/CMI but these are beyond the scope of this AusPAR.

Sponsor response

The sponsor responded to the RMP report addressing each of the issues raised. The RMP evaluator subsequently recommended to the Delegate that the Sponsor be requested to:

- provide the updated version of the aliskiren/amlodipine RMP (January 2011)
- provide the current aliskiren RMP
- provide Periodic Safety Update Report 6 for Rasilez (aliskiren)
- clarify the status of the planned database cohort study to assess the incidence of ischaemic colitis in adult treated hypertensive patients, and provide the study results when available.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

The quality evaluator recommended approval with respect to chemistry and quality control. In relation to bioavailability, it was noted that the fixed dose combination can be used as replacement therapy for patients already taking both monotherapies, there is a possible small interaction for aliskiren on amlodipine and that a high fat meal reduces the bioavailability of aliskiren. The PSC also considered this submission and had no objections on pharmaceutic or biopharmaceutic grounds but had a number of comments including a lack of support for multiple tradenames. The sponsor had initially proposed two tradenames and the second name was withdrawn. The PSC supported the sponsor's justification for the use of overseas sourced amlodipine tablet formulations, instead of the innovator brand of amlodipine monotherapy tablets available in Australia, as comparators in three of the four bioavailability studies and the pharmacokinetic interaction study. The PSC noted the significant effect of food on the bioavailability of aliskiren and also the possibility of an interaction on the aliskiren response by amlodipine.

Four bioavailability studies were submitted along with a pharmacokinetic interaction study:

- The fixed dose tablet of 300/10 mg aliskiren/amlodipine was found to be bioequivalent with the free combination of 300 mg aliskiren and 2x5 mg amlodipine.
- The fixed dose tablet of 150/10 mg aliskiren/amlodipine was found to be bioequivalent with the free combination of 150 mg aliskiren and 2x5 mg amlodipine.
- Food (high fat breakfast) delayed the absorption of aliskiren from 1.5 to 3 h for T_{max}, reduced C_{max} by 90% and AUC by 80% compared to fasted conditions. Amlodipine's absorption was delayed with food but its C_{max} and AUC were unchanged compared to the fasted state.
- A pharmacokinetic study did not reveal an interaction for amlodipine but showed a 29% increase in aliskiren levels in the presence of amlodipine with a 90% CIs of 0.83-1.69 and 1.07-1.55 for C_{max} and AUC_{0-t} respectively.

Nonclinical

The nonclinical evaluator had no objections to the registration of aliskiren/amlodipine for the proposed indication. The data package was a suitable bridging package that consisted of a 2 week and 13 week oral repeat dose toxicity studies in rats and *in vitro* studies of mutagenicity and chromosomal aberration to qualify impurities. There were no pharmacokinetic interactions between aliskiren and amlodipine observed consistent with their different routes of elimination. Relative exposure in rats for aliskiren was less than the corresponding clinical exposure but systemic exposure was adequate. The toxicological profile was consistent with the individual monotherapies with no new toxicities noted. Sufficient data were provided to qualify impurities. No efficacy or pharmacodynamic data were provided.

Clinical

Clinical evaluation

The clinical evaluator reviewed the submitted data, which relies on 4 bioequivalence studies, 7 clinical studies and a Risk Management Plan. The clinical program included 5570 patients with mild to moderate hypertension of whom 2835 received at least one dose of aliskiren/amlodipine combination and 612 patients received treatment for at least 6 months. The dataset included:

- 1 short term placebo controlled trial
- 3 short term active controlled trials
- 1 long term controlled trial and its extension
- 1 long term uncontrolled trial

The clinical evaluator recommended approval. The concerns noted by the evaluator in this submission included:

- Lack of data in patients ≥75 years
- Lack of data in severe hypertension, secondary hypertension, severe hepatic or renal impairment, cardiovascular or cerebrovascular disorders and pregnancy

Efficacy

SPA2305

This was an 8 week randomised, double blind, placebo controlled multifactorial trial in 1688 patients with essential hypertension (463 patients with Stage 2 hypertension (≥160/100 mmHg) were given Rasilamlo) comparing nine treatment groups (150 mg or 300 mg aliskiren, 5 mg or 10 mg amlodipine, 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg aliskiren/amlodipine or placebo). The study showed all active treatments were significantly superior to placebo for change in diastolic and systolic blood pressure and all combinations were statistically superior to their monotherapies for diastolic BP with a difference of 2.3-8.2 mmHg. All combinations showed reductions in systolic pressure compared to their monotherapies with a difference of 2.2-13.2 mmHg but this was not significant for 300/10 mg vs 10 mg and 150/10 mg vs 10 mg. Response rates for the combinations were significantly greater than their monotherapies for diastolic blood pressure and mostly for systolic blood pressure except for 300/10 mg vs 10 mg and 150/10 mg vs 10 mg. Blood pressure control (<140/90 mmHg) was significantly greater for all combinations than their monotherapies. For the subset of patients who had 24 hour ambulatory measurements, all combinations significantly reduced BP compared to their monotherapies. Plasma renin concentration had increased in all combination groups. The results were consistent across the subgroups of age and gender.

SPA2303

This was an 8 week randomised, double blind, parallel trial of 300/5 mg and 300/10 mg vs 300 mg aliskiren in 820 hypertensive patients not adequately responding to 300 mg aliskiren. The study showed both combination treatments were significantly superior to aliskiren 300 mg for diastolic pressure reduction (-7.23 mmHg for 300/10 and -4.71 mmHg for 300/5) and systolic pressure reduction (-11.62 mmHg for 300/10 and -8.01 mmHg for 300/5). BP response and BP control were significantly greater for both combinations vs aliskiren 300 mg. The results were consistent across the subgroups of age and gender.

SPA2304

This was an 8 week randomised, double blind, parallel trial of 150/10 and 300/10 vs 10 mg amlodipine in 847 hypertensive patients not adequately responding to 10 mg amlodipine. The study showed both combination treatments were significantly superior to amlodipine 10 mg for diastolic pressure reduction (-3.76 mmHg for 300/10 and -1.72 mmHg for 150/10) and systolic pressure reduction (-6.22 mmHg for 300/10 and -2.81 mmHg for 150/10). BP response and BP control were significantly greater for both combinations vs amlodipine 10 mg except for diastolic BP response and BP control for the 150/10 mg combination. The results were consistent across the subgroups of age and gender.

SPP2305

This was a 6 week randomised, double blind, parallel trial of 150+5 mg (aliskiren + amlodipine separate tablets) vs 10 mg amlodipine or 5 mg amlodipine in 545 hypertensive patients not adequately responding to 5 mg amlodipine. The study showed 150+5 mg was significantly superior to amlodipine 5 mg for diastolic pressure reduction (-3.62 mmHg) however there was no significant difference to amlodipine 10 mg. The 150+5 mg was significantly superior for systolic pressure reduction (-6.02 mmHg) but again no significant difference to amlodipine 10 mg. Diastolic BP response and BP control were significantly greater for 150+5 vs amlodipine 5 mg but not for amlodipine 10 mg.

SPP2323 and SPP2323E1

The initial study was a 26 week randomised, double blind, parallel active and placebo controlled study of aliskiren forced titration to 300 mg vs HCT forced titration to 25 mg with optional open label amlodipine (if BP was not <140/90 mmHg), followed by another 26 weeks of blinded treatment, in 1124 hypertensive patients. Aliskiren was found to be non-inferior to HCT after 26 and 52 weeks and by Week 52, about half of all patients were taking add-on amlodipine, however analysis of this subgroup of patients was not undertaken.

SPA2301

This was a 54 week (2 weeks titration) open label, non-randomised, uncontrolled trial of 300/10 mg with optional HCT up to 25 mg after 72 days in 556 hypertensive patients. This was primarily a safety study with efficacy as a secondary objective. Baseline diastolic BP was 98 mmHg and systolic BP was 154 mmHg. By Week 54, the reduction in blood pressure for 300/10 mg (including 15.5% who were taking HCT) was 15.5 mmHg diastolic and 24.2 mmHg systolic, with BP control at 74%.

Safety

Exposure to a combination product was from 2835 patients with hypertension with 372 receiving treatment for 12 months. Adverse events were generally mild to moderate with slightly more severe adverse events on the combination than the monotherapy. Overall AE incidence was higher for 300/10 mg (45%) compared to other groups (31-37%) and placebo (37%) in the first trial with peripheral oedema being the most commonly reported adverse event (AE) with a similar rate between 300/10 mg (13.6%) and 10 mg amlodipine (13.8%) and lower in other groups. Diarrhoea and headache were noted to be similar or less on the combination than the monotherapies. In the short term studies, AE rates were similar between combination and monotherapy groups with peripheral oedema being the most frequent but less on combination than monotherapy groups and higher in women than men. In the long term controlled trial, overall AE incidence was higher on the combination than aliskiren monotherapy but similar to amlodipine+HCT with peripheral oedema being similar for aliskiren+amlodipine and amlodipine+HCT.

No deaths have been reported in any of the above trials and serious adverse events were low and comparable to the comparator groups. A slight decrease in haemoglobin was seen in the combination groups in two studies and a slight increase in potassium was also seen that was not greater than that seen on aliskiren. In the short term studies, the proportion of those with increased potassium was slightly higher on combination than other groups and in the long term controlled trial, the proportion of those with potassium ≥5.5 mmol/L was similar between aliskiren (6.3%) and aliskiren/amlodipine (6.9%) but this was higher than HCT or HCT+amlodipine (3.8% both). Increases in blood urea nitrogen >14.28 mmol/L was less for the combination than placebo in the short term studies. Orthostatic hypotension rates were similar between combination and amlodipine alone and less than on placebo in the first trial but in the long term trial it was higher at 15% for the combination vs 9.2% for aliskiren and 12% for HCT+amlodipine.

The incidence of adverse events in those >65 years was slightly less than in those <65 years with a similar discontinuation rate and no increase in hypotension. In the short term studies, those with moderate renal impairment (4%) showed no difference in AE incidence but one patient had renal failure and one patient had renal impairment in those with moderate renal impairment on the combination products. In the long term open label study, 4% had moderate renal impairment. Discontinuation of therapy due to AEs was highest on amlodipine monotherapy in the short term studies and highest on HCT in the long term controlled study.

Risk Management Plan

The Office of Product Review has accepted the RMP (Version 2, 5 November 2010 updated with AtQ180d) for aliskiren/amlodipine.

Risk-Benefit Analysis

Delegate Considerations

Efficacy

The efficacy data of 7 clinical trials in mild to moderate hypertension were well designed and complied with the TGA-adopted EU guideline on hypertension. The short term studies demonstrated a benefit for combination treatment over the component monotherapies and placebo and mostly showed better blood pressure control and response rates along with a dose response. Occasionally it was seen that aliskiren/amlodipine combination was not significantly superior to amlodipine alone. The long term studies demonstrated sustained reduction in BP with no evidence of tolerance resulting in loss of efficacy. Blood pressure lowering was consistent across subgroups of age (< and >65 years) and gender, however there were too few patients >75 years.

Safety and RMP

The combination product was well tolerated with no new safety signals. Safety overall was similar to the monotherapies and not dose dependent except for peripheral oedema which was the most frequent AE and related to amlodipine dose that was also more frequent in women than men and most likely to lead to discontinuation. Headache, diarrhoea, cough and dizziness were not more frequent on the combination compared to monotherapies but long term had a similar rate to HCT+amlodipine. There were a small number of severe adverse events, no deaths and less serious AEs in the short term studies but a similar rate to HCT+amlodipine in the long term studies. A small decrease in haemoglobin was seen along with a small increase in potassium that was similar to monotherapy and HCT+amlodipine. Orthostatic hypotension was higher in the long term trial than monotherapy but only slightly greater than HCT+amlodipine. A subgroup

analysis by age and gender did not show any significant differences. An acceptable RMP was submitted.

Bioequivalence and food effect

Bioequivalence was demonstrated for the combinations of 300/10 mg and 150/10 mg with their components and an acceptable justification was provided for the other strengths of 150/5 mg and 300/5 mg. An acceptable justification was also provided for using overseas sourced amlodipine which was previously accepted in other submissions. Food had a significant effect in lowering the exposure to aliskiren and the sponsor has proposed to address this with a dosing recommendation that the product be taken with a light meal. However no evidence has been presented on use with a light meal to know if it affects bioavailability and this should be addressed by the sponsor. A small possible interaction in the aliskiren response was noted in the presence of amlodipine but the clinical trial data presented did not indicate a safety concern and regular BP monitoring is part of hypertension management.

Data deficiencies

There were no studies in severe hypertension or isolated systolic hypertension. There were no studies on withdrawal effects or in patients with high cardiovascular risk factors. There are a lack of data in those over 75 years of age, with severe renal or hepatic impairment and no clinical outcome studies on cardiovascular morbidity and mortality.

List of Questions

The clinical evaluator had a list of questions for the sponsor that have been adequately addressed. Study SPA2305 included 463 patients with moderate to severe hypertension who received the combination product and demonstrated greater BP reduction with the combination than placebo and monotherapies but this subgroup was not powered to demonstrate treatment differences. Safety data from short term studies from 919 patients with moderate to severe hypertension were also provided in the submission and showed the overall AE incidence to be slightly lower for the combination groups than placebo or amlodipine groups with peripheral oedema also being lower. A 54 week gastrointestinal toxicity study using colonoscopy has been previously evaluated by the TGA.

Summary

Aliskiren/amlodipine has been investigated in a number of studies by the sponsor and an acceptable efficacy profile has been demonstrated that is consistent with the TGA-adopted EU guideline on hypertension. An acceptable safety profile was also seen that was similar to the monotherapies with no new safety signals. Peripheral oedema remains the main adverse event of concern that is related to amlodipine. There is no morbidity/mortality outcome data with aliskiren but there is a trial underway. A number of patient groups were not assessed as often occurs with combination products, but it is noted that a study in patients with severe hypertension is underway and patients with Stage 2 hypertension were given Rasilamlo in the multifactorial study.

The Delegate proposed to approve the submission for the following indication:

Rasilamlo is indicated for the treatment of hypertension. Treatment should not be initiated with these fixed dose combinations.

The sponsor should address the following issues in the Pre-ACPM response:

- Provide an update on study SPA2306 and when it will be available for submission along with an update on studies of aliskiren in renal failure, gastrointestinal toxicity and the clinical outcome study in patients with hypertension that was a condition of registration for aliskiren.

- Provide an update on the status of the planned database study to assess ischaemic colitis and clarify when the next version of the RMP, due early 2011, will be submitted to OPR.
- PSUR 6 for aliskiren was requested by the OPR in relation to ventricular arrhythmias, hypertensive crises and severe hyponatraemia. Please discuss with the OPR on a suitable timeframe for submission of this PSUR.
- It was noted that the tablets containing 300 mg aliskiren are large at 21x8.3 mm. Please discuss if during the clinical trials there were any reports of difficulty swallowing these tablets, given they are not scored and will be used in the elderly.

Response from Sponsor

The sponsor responded to the questions asked by the Delegate.

Update on Study SPA2306

An update on the study in moderate to severe hypertension (study SPA100A2306) as well as updates on studies of aliskiren in renal failure (study SPP100A2262), gastrointestinal toxicity (study CSPP100A2404) and on the clinical outcome study in patients with hypertension that was a condition of registration for aliskiren (study SPP100G2301) were provided.

Study SPA100A2306

Study SPA100A2306 has completed and the full study report was available for review. The sponsor indicated it would provide the study report to the TGA for review following the finalisation of this application. For the sake of clarity and completeness, a summary of the principal findings were presented.

This study was an 8 week, double blind, randomized, parallel group, multicenter study comparing the efficacy and safety of the combination of aliskiren/amlodipine 300/10 mg as first line treatment to amlodipine 10 mg monotherapy in patients with moderate to severe hypertension (defined as msSBP1 ≥ 160 mmHg and < 200 mmHg). Patients were required to taper off their previous antihypertensive medication prior to entering the treatment phase of the study.

A total of 485 patients were randomized and entered the double blind treatment phase (244 to aliskiren/amlodipine combination therapy and 241 to amlodipine monotherapy). For the primary efficacy analysis, the combination of aliskiren/amlodipine 300/10 mg demonstrated a clinically meaningful and statistically significantly greater ($p<0.0001$) reduction in msSBP at endpoint (37.72 mmHg) compared to amlodipine 10 mg monotherapy (30.63 mmHg). A clinically meaningful and statistically significant greater ($p<0.0001$) reduction in msDBP2 was also demonstrated with aliskiren/amlodipine 300/10 mg group (16.10 mmHg) compared to amlodipine 10 mg monotherapy (12.27 mmHg) at endpoint.

Significantly more patients in the aliskiren/amlodipine 300/10 mg combination group achieved BP control at endpoint than in the amlodipine 10 mg monotherapy group (67% vs. 49%; $p=0.0001$). Plasma renin activity was also reduced by the combination of aliskiren/amlodipine (a 61.4% decrease of the geometric mean) at endpoint.

The safety results from Study SPA100A2306 showed that both treatments were well tolerated. There were no deaths in the study. No SAEs were reported with aliskiren/amlodipine, while the amlodipine monotherapy group had 3 patients with SAEs. The overall rates of AEs during the double blind period were similar in both treatment groups (48.6% for aliskiren/amlodipine; 48.1% for amlodipine monotherapy).

Discontinuations due to AEs (serious and non-serious) occurred at 2.9% in the aliskiren/amlodipine group and 6.6% in the amlodipine monotherapy group.

The approved US Prescribing Information (USPI) contains the following statements with regards to this additional double blind, active-controlled study:

[...] TEKAMLO3 was administered as initial therapy in patients with moderate to severe hypertension (SBP 160-200 mmHg). Patients were randomized to receive either combination aliskiren/amlodipine or amlodipine monotherapy. The initial dose of aliskiren/amlodipine was 150 mg/5 mg for 1 week with forced titration to 300 mg/10 mg for 7 weeks. The initial dose of amlodipine was 5 mg for 1 week with forced titration to 10 mg for 7 weeks." [...] "at the primary endpoint of 8 weeks, the treatment difference between aliskiren/amlodipine and amlodipine was 7.1/3.8 mmHg.

Study SPP100A2262

Study SPP100A2262 is an open label, parallel group, single sequence study to evaluate the pharmacokinetics, safety and tolerability of a single dose administration of 300 mg aliskiren in patients with End Stage Renal Disease (ESRD) on haemodialysis and matched healthy subjects. The study has completed the treatment phase and the final study report was expected to be available in May 2011.

Preliminary data from the study demonstrate that compared to matched healthy subjects, a single oral dose administration of 300 mg aliskiren in ESRD patients receiving haemodialysis was associated with an increase in AUC and C_{max} of 34-61% and 17%, respectively, irrespective of the time of haemodialysis. The dialysis clearance was low (1-2% of oral clearance) and the fraction of aliskiren eliminated by haemodialysis was <0.2%. A single oral dose aliskiren was well tolerated and safe in ESRD patients and healthy subjects and no AEs, SAEs or deaths were reported during the study.

Study CSPP100A2404

The full study report has been finalised and was under evaluation by the TGA as part of an application to update the Rasilez (aliskiren) PI. Upon approval of the revised Rasilez PI, the sponsor intended to submit applications to update the combination PIs.

Study SPP100G2301 (APOLLO)

The aliskiren condition of registration, commended Novartis to "commence a clinical outcome study with aliskiren in patients with hypertension within two years of registration of aliskiren". The clinical outcome study initiated to fulfil the commitment is APOLLO, a large morbidity and mortality study designed to assess the effectiveness of aliskiren based therapy (as monotherapy, with amlodipine, or with HCT) compared to a non-aliskiren based regimen, when used on top of other non-study blood pressure lowering agents in reducing the risk of major cardiovascular events in elderly hypertensive patients. It was anticipated to enrol a total of 11,000 patients over the next 2 years, with an expected follow up of 5 years. To date, over 50 patients have been recruited.

Conclusions

Preliminary and final data coming from areas of further study of the combination therapy (such as study in moderate and severe hypertension) as well as with aliskiren monotherapy (such as renal failure and gastrointestinal toxicity study) do not alter the positive risk benefit balance of aliskiren already established. Data from completed trials have been submitted to TGA for review, while data from ongoing trials will be submitted to TGA once they are completed.

Update on Database Study and RMP

An updated Version 2 of the Rasilamlo RMP was submitted to the OPR as part of the sponsor's response to the RMP evaluation. The updated pharmacovigilance plan mentioned a proposed database cohort study to assess the Incidence Rate (IR) of ischaemic colitis (IC) in adult treated hypertensive patients. This retrospective study has been now completed recently and a study report was now available upon request. Details of the analysis are summarised below.

The data source was a subset of hypertensive patients derived from the LifeLink Health Plan Claims Database, a large US health claims database. Subjects over 18 years of age with a recorded diagnosis of primary hypertension and evidence of antihypertensive drug use were identified from this subset of the LifeLink Health Plan Claims Database. Individuals were followed up from their index date, defined as the date of the first prescription of an antihypertensive treatment posterior to the first diagnosis of hypertension between 1 January 2000 and 31 December 2006, until the earliest of the following (end of follow up).

Recorded diagnosis of IC, end of enrolment in the database, end of study period, recorded claim for acute pancreatitis, or infectious gastroenteritis (based on corresponding ICD-9 codes) or recorded claim for any procedural records for surgery associated with the occurrence of IC (for example, gallbladder surgery, hysterectomy/gynaecological surgery, stomach or small bowel surgery, cancer surgery etc [identified based on CPT-4 codes]).

IC cases were identified if they had an ICD-9 code 557.xx ("vascular insufficiency of intestine") recorded during inpatient stays or outpatient visits within 3 months after a colonoscopy or colectomy. Antihypertensive exposure was classified according to the antihypertensive treatment taken during the 30 days prior to the end of follow up (last drug).

Patients were also classified according to their index antihypertensive therapy. Based upon their index drug(s), patients were classified as monotherapy, dual combination or triple combination initiators.

The overall, as well as age and sex stratified IRs including 95% CI of IC in the overall hypertensive population were calculated as the number of cases with probable IC relative to the total person time of follow up for the overall hypertensive population and the age- and sex-stratified subpopulations. Additionally, the analysis was stratified based on the initial (index) drug cohort and the last prescription prior to the end of follow up. The analysis focused on a sub-cohort of patients with a hypertensive diagnosis during the study period followed by an antihypertensive treatment and who did not have any recorded code for hypertension and/or have any prescription for an antihypertensive drug in the 6 months prior to the index date.

Out of a total of 898,877 patients initially identified as meeting the inclusion criteria, approximately 24% of subjects were excluded because they did not meet the definitions required for the analysis. Overall, 681,382 (75.80 %) subjects were included in the final analysis. Within this population, 628,427 patients (mean age 49 years [range 18-97], 51% males) were classified with a first recorded diagnosis of hypertension within the study period.

In this subpopulation, a total of 123 probable IC cases were identified corresponding to an overall IR of IC of 13.11 per 100,000 person years (95% CI: 10.99-15.65). Females had a higher IR of IC (17.86 [95% CI 14.41-22.15] per 100,000 person years) as compared to males (8.45 [95% CI 6.20-11.52] per 100,000 person years) and the IR increased by age from 6.04 (95% CI: 1.51-24.13) in the youngest age category (18-29 years) up to 42.24 (95% CI: 23.99-74.38) per 100,000 person years in the oldest age category (≥ 70 years).

Subjects with triple combination therapy – as the prescription closest to the IC diagnosis – had an IR of IC of 22.49 per 100,000 person years (95% CI: 14.17-35.70). Subjects not on treatment prior to an IC diagnosis had an IR of 4.82 per 100,000 person years (95% CI: 2.95-7.87). When stratified by index prescription, triple combination initiators had an IR of 19.86 per 100,000 person years (95% CI: 9.47-41.66) compared to an IR of 12.38 per 100,000 person-years in monotherapy initiators (95% CI: 9.97-15.37).

The results identified in this descriptive cohort study in patients with a first recorded diagnosis of hypertension based on information from a large US health claims database are compatible with results from published studies which showed an incidence rate of ischaemic colitis in the general population ranging from 4.5 to 44 cases per 100,000 person-years. The lack of an unique ICD-9 code limited to ischaemic colitis may however have lead to the inclusion of cases of intestinal ischaemia not affecting the colon and therefore to an overestimate of the true ischaemic colitis incidence. Additionally, the data source used for this analysis, does not allow the review of medical records for case validation.

In summary, the results of this analysis suggest that the incidence rate of ischaemic colitis in a treated hypertensive population is consistent with incidence rates in the general population reported in published studies. The analysis confirms that the incidence rate of ischaemic colitis in the hypertensive population is higher in females, older age groups, and patients on combination therapy.

PSUR6

PSUR6 had been submitted.

Tablet size

The sponsor confirmed that data on patients who had difficulty swallowing tablets are typically not collected as AEs. However, the sponsor was not aware of any anecdotal reports from the Rasilamlo clinical program to indicate any difficulties with swallowing the tablets. Indeed, the available drug compliance data for the Rasilamlo clinical studies indicated a similar level of compliance to what is normally expected in this population.

The sponsor also discussed aspects of the proposed PI but these are beyond the scope of this AusPAR.

In conclusion, the sponsor welcomed the Delegate's recommendation to approve Rasilamlo for the treatment of hypertension based on the evaluation of the dataset available at the time of submission. The positive benefit risk balance of aliskiren and the aliskiren combinations has since then been confirmed by preliminary and final data from areas of further study in moderate and severe hypertension, renal failure and gastrointestinal toxicity.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indication:

Rasilamlo is indicated for the treatment of hypertension. Treatment should not be initiated with these fixed dose combinations.

In making this recommendation, the ACPM considered past regulatory and postmarket experience with both actives and the clinical rationale for the combination based mainly on complementary mechanisms of action and clinical profiles.

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy, including seven clinical trials, considered there is a favourable benefit-risk profile for this product for the proposed indication. However, it was noted that there is little clinical outcome data in the elderly, in renal impairment or on cardiovascular morbidity or mortality.

The ACPM was concerned about absorption, especially in the elderly, considering the size of the tablet and the likelihood of breakage or crushing for this age group.

The Committee noted that the proposed long term study of safety and efficacy on 5000 subjects has only recently commenced.

The Committee also recommended a number of changes to be considered to the Product Information (PI) and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Rasilamlo 150/5, Rasilamlo 150/10, Rasilamlo 300/5 and Rasilamlo 300/10 film coated tablets containing aliskiren/amlodipine 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg indicated for:

Rasilamlo is indicated for the treatment of hypertension. Treatment should not be initiated with these fixed dose combinations.

Included among specific conditions of registration were the following:

- The implementation in Australia of the aliskiren/amlodipine Risk Management Plan (RMP), version 2, dated 5 November 2010 with update AtQ180d and any subsequent revisions, as agreed with the TGA and its Office of Product Review.
- The submission of clinical data when available, as category 1 submissions, for the use of aliskiren in patients with moderate to severe hypertension, end stage renal disease and ischaemic colitis (database study).
- The submission of clinical data when available, as category 1 submissions, that was requested in relation to the original aliskiren monotherapy registration, including clinical outcome study (SPP100G2301).

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

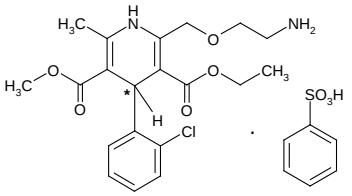
RASILAMLO 150/5®
RASILAMLO 150/10®
RASILAMLO 300/5®
RASILAMLO 300/10®

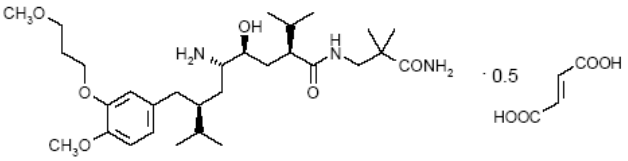
(amlodipine besylate/aliskiren hemifumarate)

NAME OF THE MEDICINE

Active ingredients (INN): amlodipine besylate, aliskiren hemifumarate

Structural formula:





and enantiomer

Amlodipine (as the besylate salt)

3-ethyl 5-methyl (4RS)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate besylate

CAS: 111470-99-6

Molecular formula: $C_{20}H_{25}ClN_2O_5,C_6H_6O_3S$

Molecular weight: 567.06

Aliskiren (as 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 hemifumarate

CAS: 173334-58-2

Molecular formula: $C_{30}H_{53}N_3O_6$, 0.5 $C_4H_4O_4$

Molecular weight: 609.8 (551.8 as free base)

DESCRIPTION

RASILAMLO® aliskiren hemifumarate/amlodipine besylate is available in four strengths: RASILAMLO 150/5®, RASILAMLO 150/10®, RASILAMLO300/5® and RASILAMLO 300/10®.

Active ingredients: Amlodipine besylate is a white or almost white powder that is slightly soluble in water and sparingly soluble in ethanol. Aliskiren hemifumarate is a white to slightly yellowish powder. It is freely soluble in water, over a wide range of pH.

Excipients: Cellulose microcrystalline, crospovidone, povidone, silica - colloidal anhydrous, magnesium stearate, hypromellose, titanium dioxide (except RASILAMLO 300/10 mg tablets),

yellow iron oxide (CI 77492), macrogol 4000 and purified talc. RASILAMLO 150/5 mg tablets also contain red iron oxide (CI 77491).

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Renin inhibitor (aliskiren) combinations with dihydropyridine derivatives (amlodipine).

Aliskiren/amlodipine

The use of combined treatment of aliskiren and amlodipine arise from the actions of these two agents on different, but complementary systems that regulate blood pressure. Calcium channel blockers act to prevent the influx of calcium into the vascular smooth muscle cells in the vessel wall, thereby preventing smooth muscle cell contraction and vasoconstriction. Renin inhibitors suppress the enzymatic activity of renin, and thereby block the formation of angiotensin II, the major effector molecule of the Renin-Angiotensin-Aldosterone System (RAAS). Angiotensin II causes vasoconstriction, and sodium and water reabsorption. Thus, amlodipine directly inhibits vasoconstriction and reduces vascular resistance, while aliskiren, by controlling angiotensin II production, can also inhibit vasoconstriction but additionally shifts water and sodium balance toward levels necessary for normotensive conditions. The combined action of aliskiren and amlodipine on these two central BP-regulating factors (vasoconstriction and RAAS-mediated hypertensive effects) results in more effective antihypertensive effects than seen with monotherapy.

Aliskiren

Aliskiren is an orally active, non peptide inhibitor of renin. Aliskiren has a higher inhibitory activity for human renin compared to other animal species. Renin is secreted by the kidney in response to decreases in blood volume and renal perfusion. This response initiates a cycle that includes the renin angiotensin system (RAS) and a homeostatic feedback loop. Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I). Ang I is converted to the active octapeptide angiotensin II (Ang II) by angiotensin-converting enzyme (ACE) and non-ACE pathways. Ang II is a powerful vasoconstrictor and leads to the release of catecholamines from the adrenal medulla and prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. Together, these effects increase blood pressure. Chronic increases in Ang II result in the expression of markers and mediators of inflammation and fibrosis that are associated with end organ damage. Ang II also inhibits renin release, thus providing a negative feedback to the system. Elevated plasma renin activity (PRA) has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients.

All agents that inhibit this system, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentration. When this rise occurs during treatment with ACE inhibitors and angiotensin receptor blockers (ARBs), it is accompanied by increased levels of PRA. During treatment with aliskiren, however, the feedback loop effects are neutralised. As a result, PRA, Ang I, and Ang II are all reduced, whether aliskiren is used as monotherapy or in combination with other antihypertensive agents. The clinical implications of differences in PRA levels are not known at present.

Treatment with aliskiren decreases PRA in hypertensive patients. In clinical trials, PRA reductions ranged from approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive drugs.

Amlodipine

The amlodipine component of RASILAMLO inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Plasma concentrations correlate with effect in both young and elderly patients. In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria. As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans. Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Pharmacokinetics

Aliskiren/amlodipine

Following oral administration of the aliskiren/amlodipine combination tablets, the median peak plasma concentration times are within 3.0 hours for aliskiren and 8.0 hours for amlodipine. The rate and extent of absorption of aliskiren and amlodipine from RASILAMLO are the same as when administered as individual tablets. A pharmacokinetic study did not reveal an interaction for amlodipine but showed a 29% increase in aliskiren levels in the presence of amlodipine with a 90% CIs of [0.83-1.69] and [1.07-1.55] for C_{max} and AUC_{0-t} respectively.

When taken with food, mean AUC and C_{max} of aliskiren are decreased by 79% and 90%, respectively, while there is no impact of food on the AUC and C_{max} of amlodipine. Patients should establish a routine pattern for taking RASILAMLO with regard to meals. Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially (see DOSAGE AND ADMINISTRATION").

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 C_{max}, 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.

Amlodipine

After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins in hypertensive patients.

Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites.

Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

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

Pharmacokinetics in the elderly: Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing

increases in AUC and elimination half-life. No initial dose adjustment of aliskiren is required for elderly patients.

Aliskiren: The AUC is 50% higher in elderly (>65 years) than in young subjects. Adjustment of the starting dose is not required in these patients (see 'DOSAGE AND ADMINISTRATION').

Pharmacokinetics in patients with impaired renal function: Amlodipine is extensively metabolised to inactive metabolites with 10% excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine may be used in such patients at normal doses. Amlodipine is not dialysable.

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Relative AUC and C_{max} of aliskiren in subjects with renal impairment ranged between 0.8 to 2-fold compared to those in healthy subjects following single dose administration and at steady state. These observed changes, however, did not correlate with the severity of renal impairment. No initial dosage adjustment of aliskiren is required in patients with mild to severe renal impairment however caution should be exercised in severe renally impaired patients.

Pharmacokinetics in patients with impaired hepatic function: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60% in AUC. In a small number of patients with mild to moderate hepatic impairment (Child-Pugh score 5-9) given single doses of 5 mg, amlodipine half-life has been prolonged. Worsening of liver function test values may occur. Amlodipine should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see DOSAGE AND ADMINISTRATION).

The pharmacokinetics of aliskiren were not significantly affected in patients with mild to moderate liver disease. Consequently, no initial dose adjustment of RASILAMLO is required in patients with mild to moderate hepatic impairment (Child-Pugh score 5-9).

CLINICAL TRIALS

In hypertensive patients, once-daily administration of RASILAMLO provided dose-dependent clinically meaningful reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval.

RASILAMLO results in greater blood pressure reductions after one week of treatment than the component monotherapies and a near-maximal effect is achieved after two to four weeks of therapy. The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity.

RASILAMLO was studied in a number of active and placebo-controlled trials and long-term trials which included a total of 5570 hypertensive patients with mild to moderate hypertension (diastolic blood pressure between 90 mmHg and 109 mmHg).

The pivotal efficacy study was of placebo-controlled and multi-factorial design which included a total of 1688 randomized patients with mild to moderate hypertension. The majority of patients were less than 65 years of age. A large number of patients were obese (46%), had metabolic syndrome (46%) and 11% of the total population had diabetes. Caucasian patients accounted for the majority of patients, with up to 20% representation from a number of ethnic groups including Hispanic or Latino patients. Approximately 20% of patients were black.

In this study, RASILAMLO in doses from 150/5 mg to 300/10 mg produced dose-dependent mean blood pressure reductions (systolic/diastolic) ranging between 20.6/14.0 mmHg and 23.9/16.5 mmHg, respectively, compared to 6.8/5.4 mmHg with placebo and compared to 15.4/10.2 mmHg for aliskiren 300 mg, 21.0/13.8 mmHg for amlodipine 10 mg in a population of patients with mean baseline blood pressure of 157.3/99.7 mmHg. In a subpopulation of 463 patients with stage 2 hypertension (SBP >=160 mmHg or DBP >= 100 mmHg), the reduction in blood pressure from baseline for RASILAMLO ranged from 25.0/15.0 to 26.7/17.5 mmHg. The blood pressure reductions with these combination doses were significantly greater than for the respective doses of aliskiren and placebo. RASILAMLO was associated with a reduction in plasma renin activity (PRA) (55-68 % reduction) versus baseline while amlodipine was associated with an increase in PRA (59-73% increase). A similar reduction in PRA was observed with aliskiren monotherapy. No significant effects of RASILAMLO were observed on the lipid profile, glucose level or weight gain.

When administered as initial therapy, RASILAMLO in doses from 150/5 mg to 300/10 mg demonstrated significantly greater systolic/diastolic blood pressure control rates (< 140/90 mmHg) as compared to the respective monotherapies with control rates ranging from 49.2% for 150/5 mg to 68.3% for 300/10 mg. A total of 84.7% of patients receiving RASILAMLO 300 mg/10 mg had a either a reduction in diastolic blood pressure to < 90 mm Hg or a ≥ 10 mm Hg decrease compared to baseline.

Efficacy of RASILAMLO was maintained over one year of treatment, with no evidence of loss of effect.

In a study in 820 randomised patients not adequately responsive to aliskiren 300 mg treatment, the combination of aliskiren/amlodipine 300/10 mg produced systolic/diastolic mean blood pressure reductions of 18.0/13.1 mmHg, which were statistically significantly greater than aliskiren 300 mg monotherapy. The combination at a dose of 300/5 mg also showed statistically significantly greater blood pressure reduction than aliskiren 300 mg monotherapy.

In a study in 847 randomised patients not adequately responsive to amlodipine 10 mg treatment, the combination of aliskiren/amlodipine 300/10 mg produced systolic/diastolic mean blood pressure reductions of 14.4/11.0 mmHg, which were significantly greater than for amlodipine 10 mg monotherapy. The combination at a dose of 150/10 mg also showed significantly greater blood pressure reduction than amlodipine 10 mg monotherapy. In another study in 545 randomized patients not adequately responsive to 5 mg amlodipine, the combination of aliskiren 150 mg/amlodipine 5 mg resulted in a blood pressure reduction of 11.0/ 8.5 mm Hg compared to 9.6 / 8.0 mm Hg for amlodipine 10 mg (not statistically significant) and was associated with a lower incidence of peripheral oedema (aliskiren/amlodipine: 2.1%; amlodipine 5 mg: 3.4%; amlodipine 10 mg: 11.2%) .

Other:

There is a lack of clinical data in patients with renal failure, isolated systolic hypertension and left ventricular hypertrophy. The combination of aliskiren and amlodipine has not been studied in patients with secondary hypertension. No clinical outcome studies have been conducted on cardiovascular morbidity and mortality with RASILAMLO.

INDICATIONS

RASILAMLO is indicated for the treatment of hypertension. Treatment should not be initiated with these fixed dose combinations.

CONTRAINDICATIONS

- Hypersensitivity to the active substances, dihydropyridine derivatives, or to any of the excipients;
- Pregnancy;
- History of angioedema with aliskiren;
- Hereditary or idiopathic angioedema;
- Severe hypotension;
- Shock (including cardiogenic shock);
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis);
- Haemodynamically unstable heart failure after acute myocardial infarction;
- Concomitant administration with cyclosporine, a highly potent P-gp inhibitor, and other potent P-gp inhibitors such as verapamil, quinidine and itraconazole (see 'PRECAUTIONS - Interactions with Other Drugs').

PRECAUTIONS

Hypersensitivity: RASILAMLO should not be used in patients with known hypersensitivity to aliskiren or amlodipine (or other dihydropyridine derivatives) or to any of the excipients (see "CONTRAINDICATIONS").

Angioedema: As with other agents acting on the renin-angiotensin system, angioedema has been reported rarely in patients treated with aliskiren. If angioedema occurs, RASILAMLO 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 a patent airway should be provided.

Hypotension: As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke. If an excessive fall in blood pressure occurs with RASILAMLO, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilised.

Concomitant use with cyclosporine A or verapamil, quinidine or itraconazole: The concomitant use of aliskiren with cyclosporine, a highly potent glycoprotein inhibitor, and other potent P-gp inhibitors such as verapamil, quinidine and itraconazole, is contraindicated.

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 RASILAMLO. This condition should be corrected prior to administration of RASILAMLO, or the treatment should start under close medical supervision. In patients with uncomplicated hypertension treated with RASILAMLO in short-term controlled trials, the incidence of hypotension was low (0.2 %).**Impaired renal function:** No adjustment of the initial dose is required for patients with mild to moderate renal impairment (30 mL/min/1.73m^2 ≤ GFR < 90 mL/min/1.73m^2).

RASILAMLO has not been studied in hypertensive patients with severe renal dysfunction (creatinine ≥150 μmol/L for women and ≥ 177 μmol/L for men and/or estimated GFR <30 mL/min/1.73m^2), a history of dialysis, nephrotic syndrome, or renovascular hypertension. Other agents that act on the renin-angiotensin system may increase potassium, serum creatinine and blood urea nitrogen in these patients and a similar effect may be anticipated with RASILAMLO. Caution should be exercised when using RASILAMLO in hypertensive patients with severe renal impairment due to the absence of safety information in this patient population.

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.

Patients receiving other medicinal products that inhibit the renin-angiotensin-aldosterone system (RAAS), and/or those with reduced kidney function and/or diabetes mellitus are at an increased risk of hyperkalaemia during aliskiren therapy. **Hepatic impairment:** Amlodipine is extensively metabolised by the liver and the plasma elimination half life is 56 hours in patient with impaired hepatic function. Worsening of the liver function test may occur. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60%. Therefore caution should be exercised when administering RASILAMLO to patients with hepatic impairment and careful monitoring should be performed.

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 RASILAMLO 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.

Increased angina: Rarely patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina on starting calcium channel blocker therapy or at the time of dosage increase.

Beta-blocker withdrawal: Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Use in patients with heart failure/Post-myocardial infarction: RASILAMLO should be used with caution in patients with heart failure due to limited clinical efficacy and safety data. Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV). In general, calcium channel blockers should be used with caution in patients with heart failure. As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death.

Care should be taken to differentiate peripheral oedema from the effects of increasing left ventricular dysfunction.

Children and adolescents: The safety and efficacy of RASILAMLO in children and adolescents (below the age of 18 years) have not been established.

Severe diarrhoea: In the event of severe and persistent diarrhoea, aliskiren/amlodipine therapy should be stopped.

Effects on ability to drive and use machines: No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles or using machines it should be taken into account that occasionally dizziness or weariness may occur.

Carcinogenicity:

No carcinogenicity studies have been conducted with the aliskiren/amlodipine combination.

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 AUC). 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 <1 and 3 based on AUC, 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 AUC). These tumour incidences were not statistically significant versus untreated controls. The results from a subsequent 104-week oral toxicity study in marmoset monkeys showed the absence of any treatment-related histopathological changes in the gastro-intestinal tract at oral doses of 10 and 20 mg/kg/day (up to 5times greater than clinical exposure to unbound aliskiren at the maximum recommended daily dose, based on AUC). Overall, the data suggests that these tumour incidences may not be clinical relevant.

Amlodipine: The carcinogenic potential of amlodipine has not been fully elucidated. Amlodipine did not induce any tumours when tested in rats at oral doses up to 2.5 mg/kg. This dose gave rise to plasma levels that are similar to those achieved clinically.

Genotoxicity

The combination of aliskiren and amlodipine was negative in *in vitro* assays of bacterial reverse mutation and chromosomal damage.Aliskiren: Aliskiren was negative in a series of assays for gene mutation, chromosomal damage and DNA damage.

Amlodipine did not induce gene mutation in bacteria or mouse lymphoma cells, and was not clastogenic in human lymphocytes, Chinese hamster V79 fibroblast cells (*in vitro*), or mouse bone marrow cells (*in vivo*).

Effects on fertility

Aliskiren: Aliskiren did not affect fertility or general reproductive performance when given to rats at oral doses up to 226 mg/kg/day (ER 1 based on AUC).

Amlodipine: There was no effect on fertility of rats treated with amlodipine at oral doses up to 18 mg/kg/day.

Use in Pregnancy (Category D)

Aliskiren

Aliskiren must not be used during pregnancy or in women planning to become pregnant. Physicians prescribing any agents acting on the RAAS (renin-angiotensin-aldosterone system) should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, RASILAMLO must 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, RASILAMLO 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 maternotoxic 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).

Amlodipine

There is no clinical experience with amlodipine in pregnancy. Animal studies have shown reproductive toxicity. The potential risk to humans is unknown.

The safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine had no teratogenic effects in rats (18 mg/kg) or rabbits (10 mg/kg). Amlodipine (7 mg/kg) administered orally to rats at or near parturition induced a prolongation of gestation time, increase in the number of stillbirths and a decreased postnatal survival. Calcium channel blockers carry the potential to produce foetal hypoxia associated with maternal hypotension. Accordingly they should not be used in pregnant women unless the potential benefit outweighs the risk to the foetus.

Use in Lactation

RASILAMLO is not recommended during lactation. It is not known whether aliskiren and/or amlodipine is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. The safety of amlodipine in human lactation has not been established. 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 RASILAMLO, taking in account the importance of both the control of hypertension and breast-feeding to the mother and infant.

Interactions with Other Drugs

RASILAMLO

Co-administration of aliskiren and amlodipine does not cause meaningful changes in the steady-state pharmacokinetic exposure (AUC) and the maximum concentration (C_{max}) of either component in healthy volunteers. No drug interaction studies have been conducted with aliskiren/amlodipine combination, although studies with the individual components are described below.

Concomitant use of RASILAMLO with other medicines that cause hypotensive effects may increase the antihypertensive effect of the combination.

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 C_{max} up to 50% after multiple dosing. Data suggest that irbesartan may decrease aliskiren AUC and C_{max}. 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 Cmax). Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. The change in plasma levels of aliskiren in the presence of ketoconazole 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. Yet, P-gp inhibitors are expected to increase tissue concentrations more than plasma concentrations. Therefore, caution should be exercised when aliskiren is administered with ketoconazole or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

Co-administration of a single oral dose of 300 mg aliskiren with 240 mg verapamil increased AUC and C_{max} of aliskiren by ~2-fold. Therefore, the concomitant use of verapamil and aliskiren is contraindicated (See "CONTRAINDICATIONS").

Pgp potent inhibitors: A single dose drug interaction study in healthy subjects has shown that cyclosporine A (200 and 600 mg) increases C_{max} of aliskiren 75 mg by approximately 2.5 fold and the AUC by approximately 5-fold. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5 fold and 5.8 fold, respectively. Therefore, the concomitant use of these drugs is contraindicated (See "CONTRAINDICATIONS").

Frusemide: When aliskiren was co-administered with frusemide, the AUC and C_{max} of frusemide 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.

Grapefruit juice: Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and C_{max} of aliskiren. Grapefruit juice should not be taken with RASILAMLO.

Amlodipine

In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin (glyceryl trinitrate), digoxin, warfarin, atorvastatin, aluminium/magnesium antacid, cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, ethanol and oral hypoglycaemic drugs.

CYP3A4 inhibitors: A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50% and the effect of amlodipine is increased). The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded. Amlodipine should be used with caution together with CYP3A4 inhibitors.

CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum): Co-administration may lead to reduced plasma concentrations of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal. Amlodipine should be used with caution together with CYP3A4 inducers.

Cyclosporine: The pharmacokinetics of cyclosporine were not altered when cyclosporine was coadministered with amlodipine in renal transplant patients. The patients were not taking corticosteroids.

Grapefruit juice: Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers. In a study in 20 healthy volunteers, coadministration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single 100 mg dose of sildenafil in 16 patients with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

ADVERSE EFFECTS

RASILAMLO has been administered to more than 2800 patients in completed clinical trials, including 372 patients for one year or more. Treatment with RASILAMLO was well tolerated at doses up to 300/10mg with an overall incidence of adverse events similar to the component monotherapies and placebo. The incidence of adverse events did not show any association with gender, age, body mass index, race or ethnicity. There were no new adverse reactions which occurred specifically with RASILAMLO in addition to those known to be associated with the individual monotherapies. Adverse events have generally been mild and transient in nature. In a double-blind, randomized placebo controlled study in 1688 patients with mild or moderate hypertension, discontinuation of therapy due to a clinical adverse event occurred in 1.7 % of patients treated with RASILAMLO versus 1.5 % of patients given placebo.

The most frequent adverse reactions for RASILAMLO are hypotension and peripheral oedema.

Peripheral oedema is a known, dose-dependent adverse reaction of amlodipine and has also been reported with aliskiren therapy in post-marketing experience. The most frequently reported adverse reaction for RASILAMLO in clinical trials was peripheral oedema, which occurred at a frequency lower than or equal to that of the corresponding amlodipine doses, but higher than with aliskiren.

Number (%) of patients with the most frequent AE (at least 2% for any treatment group) by preferred term, in short term, double blinded, all controlled studies.

Preferred term	Placebo N=198 n (%)	Mono Ali N=657 n (%)	Mono Aml N=1004 n (%)	Ali/Aml 150/5 mg N=368 n (%)	Ali/Aml 150/10 mg N=464 n (%)	Ali/Aml 300/5 mg N=454 n (%)	Ali/Aml 300/10 mg N=745 n (%)
Any AE	74(37.4)	189(28.8)	323(32.2)	119(32.3)	158(34.1)	137(30.2)	254(34.1)
Edema peripheral	2(1.0)	6(0.9)	84(8.4)	8(2.2)	37(8.0)	8(1.8)	66(8.9)
Nasopharyngitis	6(3.0)	15(2.3)	26(2.6)	4(1.1)	19(4.1)	8(1.8)	25(3.4)
Headache	20(10.1)	38(5.8)	36(3.6)	16(4.3)	11(2.4)	15(3.3)	11(1.5)
Upper respiratory tract infection	5(2.5)	10(1.5)	6(0.6)	9(2.4)	6(1.3)	7(1.5)	9(1.2)
Dizziness	3(1.5)	14(2.1)	13(1.3)	4(1.1)	4(0.9)	8(1.8)	13(1.7)

Additional information on individual components

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

Aliskiren

The following table of adverse events is based on five placebo-controlled studies involving a total of 5664 patients (Study Protocols 1201, 2201, 2203, 2204 and 2308). Of the 2316 patients receiving aliskiren monotherapy, 1542 received one of the marketed doses. All adverse events showing an incidence of 1% or more in the aliskiren group are included in the following table, irrespective of their causal association with the study drug.

	Placebo N=781 n(%)	Aliskiren 150 mg N=774 n(%)	Aliskiren 300 mg N=768 n(%)
Headache	68 (8.7)	42 (5.4)	44 (5.7)
Nasopharyngitis	45 (5.8)	33 (4.3)	29 (3.8)
Diarrhoea	9 (1.2)	9 (1.2)	18 (2.3)
Dizziness	17 (2.2)	9 (1.2)	19 (2.5)
Fatigue	12 (1.5)	5 (0.6)	13 (1.7)
Upper respiratory tract infection	12 (1.5)	7 (0.9)	13 (1.7)
Back pain	11 (1.4)	12 (1.6)	7 (0.9)
Cough	5 (0.6)	11 (1.4)	7 (0.9)
Bronchitis	3 (0.4)	6 (0.8)	9 (1.2)
Nausea	11 (1.4)	3 (0.4)	12 (1.6)
Influenza	5 (0.6)	9 (1.2)	5 (0.7)

The adverse drug reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), including isolated report. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Gastrointestinal disorders	
Common	Diarrhoea
Skin and subcutaneous tissue disorders	
Uncommon	Rash
Rare	Angioedema
Immune system disorders	
Rare	Hypersensitivity
Cardiovascular	
Uncommon	Peripheral oedema

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. No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in patients treated with aliskiren.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.81 g/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.

Other Laboratory findings: In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of Rasilez. In clinical studies in hypertensive patients, Rasilez had no clinically important effects on total cholesterol, fasting glucose or uric acid, however, minor (<1%) decreases in HDL and increases in triglycerides that were not dose related were noted.

Blood Urea Nitrogen, Creatinine: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 7% of patients with essential hypertension treated with Rasilez alone vs. 6% on placebo.

Serum Uric Acid: Aliskiren monotherapy produced small median increases in serum uric acid levels (about 6 μmol/L) while HCTZ produced larger increases (about 30 μmol/L). The combination of aliskiren with HCTZ appears to be additive (about a 40 μmol/L increase). The increases in uric acid appear to lead to slight increases in uric acid-related AEs: elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Creatine Kinase: Increases in creatine kinase of >300% were recorded in about 1% of aliskiren monotherapy patients vs. 0.5% of placebo patients. Five cases of creatine kinase rises, three leading to discontinuation and one diagnosed as subclinical rhabdomyolysis and another as myositis, were reported as adverse events with aliskiren use in the clinical trials. No cases were associated with renal dysfunction.

Post-Marketing Experience

Metabolic and Nutritional	
Unknown frequency	Blood creatinine increased
Immune system	
Unknown frequency	Hypersensitivity, angiodema requiring airway management and hospitalisation.
Skin and subcutaneous tissue disorders	
Very Rare	Stevens-Johnson syndrome*, rash
Vascular disorders	
Very rare	Necrotising vasculitis*
Cardiovascular	

Unknown frequency	Peripheral oedema

*Causality was unclear in these adverse events which occurred very rarely, were poorly documented or were confounded.

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk.

Amlodipine

The following adverse events occurred in≤ 1% but > 0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician of a possible relationship:

Vomiting, peripheral ischaemia, alopecia, anorexia, altered bowel habits, dyspepsia, dysphagia, flatulence, nausea, gingival hyperplasia, abdominal pain upper, constipation, dyspnoea, epistaxis, rhinitis, hyperglycaemia, malaise, gynaecomastia, sexual dysfunction, insomnia, anxiety, nervousness, depression, abnormal dreams, somnolence, depersonalisation, mood changes, pain, headache, rigors, weight gain, arthralgia, arthrosis, muscle cramps, myalgia, hypoesthesia, tremor, peripheral neuropathy, paraesthesia, hypotension, postural hypotension, syncope, vertigo, dizziness, pancreatitis, leucopenia, thrombocytopenia, purpura vasculitis, conjunctivitis, diplopia, eye pain, vision abnormal, tinnitus, micturition frequency and disorder, nocturia, sweating increased, dry mouth, thirst, allergic reactions, angioedema, erythema multiforme, rash maculopapular and rash erythematous.

Rarely observed adverse events (occurring in≤ 0.1% of patients) were cardiac failure, pulse irregularity, extrasystoles, skin discolouration, urticaria, skin dryness, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, increased appetite, gastritis, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, xerophthalmia and weight decrease.

There have been infrequent, post marketing reports of hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis). Some cases severe enough to require hospitalisation have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

In a long-term placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Risk of Myocardial Infarction or Increased Angina or arrhythmia: As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction, angina, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. Arrhythmia (including ventricular tachycardia and atrial fibrillation) has also been reported with calcium channel blocker

therapy. These adverse events may not be distinguishable from the natural history of the underlying disease.

DOSAGE AND ADMINISTRATION

The dose of RASILAMLO 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 RASILAMLO 150/5 or RASILAMLO 150/10 or RASILAMLO 300/5 or RASILAMLO 300/10. The maximum recommended dose of the combination therapy is 300/10 mg once daily.

The antihypertensive effect is largely manifested within 1 week and the effect is near maximal at around 2-4 weeks. If blood pressure remains uncontrolled after 2 to 4 weeks of therapy, the dose may be titrated up to the maximum daily dose. Dosing should be individualized and adjusted according to the patient's clinical response.

Patients should establish a routine pattern for taking RASILAMLO with regard to meals. Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially. Tablets should be swallowed whole with water.

Patients not adequately treated on monotherapy

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

Patients adequately treated with separate tablets of aliskiren and amlodipine

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

Co-administration with Other Antihypertensive Drugs: RASILAMLO may be co-administered with other anti-hypertensive agents such as hydrochlorothiazide.(See "Interactions with Other Drugs" for information about the individual components).

Renal impairment: No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see 'PHARMACOLOGY – Pharmacokinetics'). Care must be taken when dosing patients with severe renal impairment as there are no data in such patients.

Hepatic impairment: No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment (Child-Pugh Score 5-9; see 'PHARMACOLOGY – Pharmacokinetics'). Caution should be exercised when administering RASILAMLO to patients with hepatic impairment. The dose should be titrated slowly and care should be taken when dosing patients with severe hepatic impairment as there are no data in such patients .Small, frail and elderly patients may need to start at a low amlodipine dose.

Use in elderly patients (over 65 years): There is limited experience with RASILAMLO, in particular in patients aged 75 years or older. Therefore, particular caution should be exercised in these patients. No initial dosage adjustment is required in elderly patients.

Use in children and adolescents: The safety and efficacy of RASILAMLO has not been established in children and adolescents (below 18 years of age) and therefore RASILAMLO 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 amlodipine. If symptomatic hypotension should occur, supportive treatment should be initiated.

Overdose with amlodipine may result in excessive peripheral vasodilatation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension, including shock with fatal outcome, have been reported with amlodipine. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Amlodipine is unlikely to be removed by dialysis.

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

PRESENTATION AND STORAGE CONDITIONS

RASILAMLO 150/5: Light yellow, ovaloid convex shaped film-coated tablet with a bevelled edge with debossing “T2” on one side and “NVR” on the reverse side of the tablet. Packs of 7, 14, 28, 30 and 56.

RASILAMLO 150/10: Yellow, ovaloid convex shaped film-coated tablet with a bevelled edge with debossing “T7” on one side and “NVR” on the reverse side of the tablet. Packs of 7, 14, 28, 30 and 56.

RASILAMLO 300/5: Dark yellow, ovaloid convex shaped film-coated tablet with a bevelled edge with debossing “T11” on one side and “NVR” on the reverse side of the tablet. Packs of 7, 14, 28, 30 and 56.

RASILAMLO 300/10: Brown yellow, ovaloid convex shaped film-coated tablet with a bevelled edge with debossing “T12” on one side and “NVR” on the reverse side of the tablet. Packs of 7, 14, 28, 30 and 56.

Not all pack sizes may be marketed.

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

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

RASILAMLO is a Schedule 4 medicine.

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration: 10 June 2011

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au

Reference/Publication #