EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

for

Rasitrio

International non-proprietary name: **aliskiren / amlodipine / hydrochlorothiazide**

Procedure No. **EMEA/H/C/002017**

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

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List of abbreviations

14C	Carbon-14 radioisotope
3H	Tritium radioisotope
ABPM	ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
ACE	angiotensin-converting enzyme
ADME	Absorption, distribution, metabolism and excretion
ADR	adverse drug reaction
AE	adverse event
Al	Aluminium
Ali	aliskiren
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
Aml	amlodipine
Ang	angiotensin
AR1	Autoregressive order 1
ARB	Angiotensin receptor blocker
ARB	angiotensin receptor blocker
ATR	Attenuated Total Reflection
AUC	area under the plasma concentration-time curve
AV	atrioventricular
BA	bioavailability
BCS	Biopharmaceutics Classification System
BE	bioequivalence
BMI	body mass index
BP	Blood pressure
BSE	Bovine Spongiform Encephalopathy
BU	Blend Uniformity
BUN	blood urea nitrogen
CCB	calcium channel blocker
CEP	Certificate of Suitability of the Monograph of the European Pharmacopoeia
CFU	Colony Forming Units
CI	confidence interval
CL	Clearance
Cmax	Maximum plasma concentration
CoA	Certificate of Analysis
CU	Content Uniformity
CV	cardiovascular
CV%	coefficient of variation
CYP	Cytochrome P450 dependent enzyme, catalyzing oxidative drug metabolism
DBP	diastolic blood pressure
DDI	drug-drug interaction
DRI	direct renin inhibitor
DSC	Differential Scanning Calorimetry
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FMI	final market image
GC	Gas Chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCTZ	Hydrochlorothiazide
HPLC	High Performance Liquid Chromatography
i.v.	Intravenous injection
ICH	International Conference on Harmonisation
ICP-OES	Inductively Coupled Plasma-Optical Emission Spectroscopy
IND	Investigation New Drug
IPC	In-process control
IR	Infrared
KF	Karl Fischer
kg	Kilogram

Ki	Enzyme inhibition constant (unit: µmol/L)
LC-MS/MS	High performance liquid chromatography, coupled to tandem massspectrometry(MS2)
LLOQ	Lower limit of quantification
LOD	Limit of Detection
LOQ	(1) Limit of Quantification, (2) List of Questions
LSM	Least square means
MADBP	mean ambulatory diastolic blood pressure
MASBP	mean ambulatory systolic blood pressure
MDR1	Multi-drug resistance 1 protein (P-gp), involved in drug transport
MedDRA	Medical Dictionary for Regulatory Activities
MRP2	Multidrug resistance protein (human), involved in canalicular organic anion transport
MS	Mass Spectroscopy
msDBP	mean sitting diastolic blood pressure
msSBP	mean sitting systolic blood pressure
ND	Not detected
NIR	Near Infra Red
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOAEL	No observed adverse effect level
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
p.o.	Peroral dosing
PA	Polyamide
PCTFE	Polychlorotrifluoroethylene
Ph.Eur./ EP	European Pharmacopoeia
Ppm	parts per million
PRA	plasma renin activity
PRC	plasma renin concentration
PT-Table	post-text table
PTY	patient treatment years
PVC	Poly vinyl chloride
QT	interval (time) = interval between onset of Q-wave and end of T-wave
RAAS	renin-angiotensin-aldosterone system
RAS	Renin angiotensin system
RH	Relative Humidity
SAE	serious adverse event
SAH100	Rasitrio (aliskiren / amlodipine / hydrochlorothiazide)
SBP	systolic blood pressure
SBPS	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SOC	system organ class
SPA100	aliskiren / amlodipine combination
SPH100	aliskiren / hydrochlorothiazide combination
SPP 10	aliskiren
T1/2	Elimination half-life time of plasma concentrations
TG	Thermo-Gravimetry
THF	Tetrahydrofurane
Tmax	Time to the maximum observed plasma concentration
TSE	Transmissible Spongiform Encephalitis
UDU	Uniformity of Dosage Units
ULN	Upper Limit of Normal
USP/NF	United States Pharmacopoeia / National Formulary
UV	Ultraviolet
vs	versus
Vss	Volume of distribution at steady-state (dimension: L or L/kg)
Vz	Volume of distribution during the elimination phase (dimension: L or L/kg)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd. submitted on 10 May 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Rasitrio, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 October 2009.

The applicant applied for the following indication: treatment of essential hypertension.

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC, as amended – relating to applications for new fixed combination products

The application submitted is a new fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/236/2009 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Applicant's request(s) for consideration

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Daniela Melchiorri** Co-Rapporteur: **János Borvendég**

- The application was received by the EMA on 10 May 2010.
- The procedure started on 26 May 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 August 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 August 2010.
- During the meeting on 20-23 September 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 September 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 March 2011.
- The summary report of the GCP inspection carried out at the three investigator sites (two in Canada and one in Latvia) between 24 August and 30 September 2010 was issued on 31 October 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 and 4 May 2011.
- During the CHMP meeting on 16-19 May 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 August 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 September 2011.
- The applicant submitted the responses to the Joint Assessment Report on 15 September 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses on 16 September 2011.
- During the meeting on 19-22 September 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Rasitrio on 22 September 2011.

2. Scientific discussion

2.1. Introduction

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

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

Inhibition of the renin-angiotensin system (RAS) is an effective way to intervene in the pathogenesis of cardiovascular and renal disorders. Renin is the enzyme responsible for the conversion of

angiotensinogen to angiotensin I. The angiotensin converting enzyme (ACE) transforms angiotensin I into the active octapeptide angiotensin II, which acts *via* type-1 angiotensin II receptors (AT1) to increase arterial tone, adrenal aldosterone secretion, renal sodium re-absorption, sympathetic neurotransmission, and cellular growth.

Some of currently used antihypertensive drugs intervene at different points of renin-angiotensin system:

- β blockers reduce the release of renin from the juxtaglomerular apparatus and lower blood pressure.
- ACE-inhibitors reduce the conversion of angiotensin I to angiotensin II. They also inhibit the inactivation of bradykinin and substance P, causing some typical side-effects of ACE inhibitors, such as cough and angioedema.
- Angiotensin-receptor antagonists (ARB) block the interaction of angiotensin II with the AT1 receptor.
- Renin-inhibitors directly inhibit renin, blocking the RAS at its very origin.

Despite the availability of several therapeutic choices, in a large portion of hypertensive patients blood pressure cannot be adequately controlled by one antihypertensive drug alone. For the majority of patients, a combination of two or more antihypertensive medications will be required to reach an adequate blood pressure control. In this scenario, development of new fixed-dose combinations of different antihypertensive drugs helps to improve patient compliance over the free combination of the single monotherapies and the safety profile related to the current available treatments.

This is an application for aliskiren/amlodipine/hydrochlorothiazide fixed combination at doses of 150 mg/5 mg/12.5 mg, 300 mg/5 mg/12.5 mg, 300 mg/5 mg/25 mg, 300 mg/10 mg/12.5 mg, 300 mg/10 mg/25 mg proposed as substitution therapy in adult patients adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide, taken either as three single-component formulations or as a dual-component and a single-component formulation, given concurrently, at the same dose level as in the combination.

2.2. Quality aspects

2.2.1. Introduction

Rasitrio film-coated tablet is a new fixed combination medicinal product that combines two antihypertensive compounds, aliskiren and amlodipine, with complementary mechanisms, and a diuretic, hydrochlorothiazide (HCTZ), to control blood pressure in patients with hypertension.

The claimed indication concerns the use of the FDC 150 mg/5 mg/12.5 mg, 300 mg/5 mg/12.5 mg, 300 mg/5 mg/25 mg, 300 mg/10 mg/12.5 mg, 300 mg/10 mg/25 mg as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently at the same dose level as in the combination.

Aliskiren hemifumarate (SPP100) is an anti-hypertensive agent that inhibits the renin-angiotensin system and Amlodipine besylate is a dihydropyridine calcium channel blocker. Hydrochlorothiazide (HCTZ) is a well-known thiazide diuretic commonly used for the treatment of hypertension, thanks to its effect on volume/sodium depletion. Aliskiren hemifumarate, amlodipine besylate and HCTZ are already present in mono and combination products already approved.

The combination of a direct-renin inhibitor, a calcium channel blocker, and a thiazide diuretic is considered as logical because the mechanisms of action of the 3 drugs are complementary, each typically working on a separate mechanism, thus blocking different effector pathways. This fixed combination of aliskiren/amlodipine/HCTZ has been developed since a number of hypertensive patients require three or more antihypertensive drugs to achieve adequate blood pressure control.

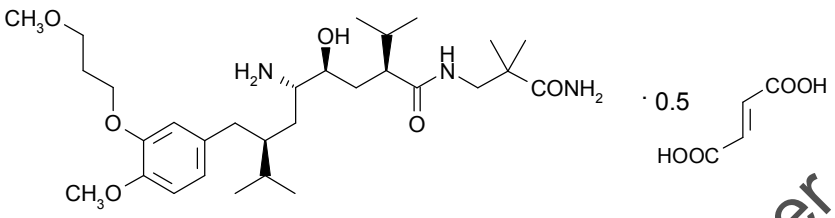
The primary packaging for the tablets consists of Polyamide/Aluminium/Polyvinylchloride (PA/AL/PVC) blister packs (Alu blisters) and Polytetrafluoroethylene (PCTFE)/PVC blister packs backed with a heat sealable lacquered aluminium foil

2.2.2. Active Substance

Drug Substance (to be changed in the EPAR to "Active Substance") Aliskiren hemifumarate

Aliskiren hemifumarate has already been authorized via the centralised procedure both in monotherapy and in combination products, owned by the Applicant Novartis for Rasilez (product number EMEA/H/C/000780 authorised on 22/08/2007).

Aliskiren hemifumarate exists as a white to slightly yellowish powder. It has four chiral centres, but is obtained as a single diastereoisomer, all S-configured.
Sufficient scientific information has been presented for the physicochemical properties such as appearance, solubility in standard aqueous buffers and non-aqueous solvents, pKa, specific rotation, log P, melting point and thermal behaviour.
This molecule shows polymorphs.



Manufacture

Aliskiren hemifumarate (SPP100) is manufactured according to two synthetic pathways: routes B and C.

The active substance is manufactured with total synthesis including ten and six main stages using routes [synB] and [synC], respectively. Addition of synthesis C in alternative to synthesis B has been the object of a type II variation (EMEA/H/000780/II/0002 and follow up). The alternate synthesis C has been developed to reduce the complexity of the process, while improving the overall quality and safety.

Adequate in-process controls including the control of the stereochemistry and control of the critical steps have been applied as well as controls of the reagents, solvents, catalysts, starting materials, and intermediates used in the manufacture of aliskiren hemifumarate. Materials used in the manufacture of aliskiren hemifumarate are all of synthetic origin; therefore do not pose a risk of TSE/BSE contamination.
Adequate specification has been included for the starting materials, solvents, and intermediates.
Validation data are available and the robustness of the process has been demonstrated.
The structure of aliskiren hemifumarate (SPP100) is supported by the synthetic routes. Its structure has been fully elucidated with usual techniques such as elementary analysis, Infra-Red (IR) spectroscopy, Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR) spectroscopy, mass spectroscopy (by ESI, Electron Spray Ionisation) and X-ray powder diffractometry (XRPD), optical rotation (single diasteroisomer), particle size analysis.

Specification
The active substance specification using the different syntheses differs only in the requirements for residual solvents and impurities.
Appropriate specification has been set up for the active substance obtained by route B and route C and includes appearance, particle size, appearance of the solution, identification (IR, XR and optical rotation), residual solvents (Gas Chromatography GC), water content, sulfated ash, heavy metals, related substances, assay (titration and HPLC), assay of the salt (fumaric acid), microbiological quality. The skip-testing approach for the microbiological quality is considered acceptable.

Specification of the active substance including residual solvents (in line with ICH requirements) and impurities (justified by toxicological data) was appropriately justified. An overview on the related substances of aliskiren hemifumarate has been presented covering potential process impurities and degradation products (from synthesis B and C). Levels observed and the origin of related substances has been extensively discussed and found satisfactory. The limits are in line with ICH Q3A. The level of polymorphs is adequately controlled

Analytical methods have been adequately detailed and non-compendial methods validated in accordance with ICH guidelines.
The bulk of the active substance is packed in very tight packaging. The bags are stored in drums with a tamper resistant seal.

Batch analysis from batches obtained by the route B (12 batches) and the route C (6 batches) has demonstrated the uniformity and the consistency of the syntheses.
Data presented show the release testing of batches manufactured by syntheses B and A which were used in clinical trials, toxicological studies and / or primary stability studies. Comparative analytical data of three more recent batches of aliskiren hemifumarate manufactured by the synthetic route B and three batches of drug substance manufactured by the synthetic route C. All the results were found compliant with the specification.

Stability

Stability summary and conclusions for synthesis B

Stability data on three pilot batches have been carried out under ICH long term (24 months, 25°C/60%RH) and accelerated conditions (6 months, 40°C/75%RH) as well as photostability and stress testing under different conditions. Very tight packaging has to be used.
In addition six production batches have been placed under stability. The stability reports submitted contain data covering 36 months of long term and 6 months of accelerated stability studies.

The parameters tested were including: appearance, identity (IR, X-ray diffraction, optical rotation), impurities (HPLC), water content (Karl-Fischer), clarity and colour of the solution and assay (HPLC). All parameters were found in accordance with the specification and no major degradation could be observed under long-term and accelerated conditions.

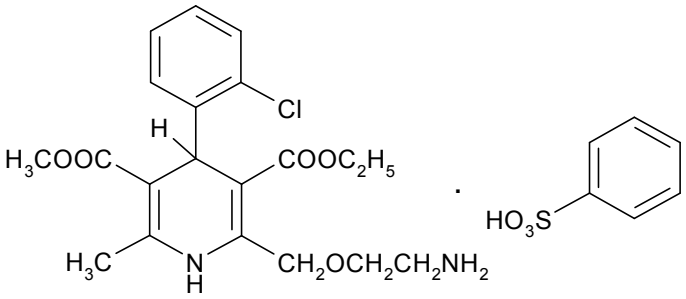
Stability summary and conclusions for synthesis C

Stability data on four development batches and three production-scale batches have been carried out under ICH long term and accelerated conditions (24 months, 25°C/60%RH, 30°C/ 65% RH and 40°C/ 75% RH and 18 months respectively). The results obtained show that they are similar to the data obtained for aliskiren hemifumarate manufactured by synthesis B and confirm the storage precautions (store below 25°C, protect from light in very tight packaging).

Based on the discussion above, the data for synthesis B support a retest period of 30 months stored not above 25°C in a very tight packaging. Stability data on pilot and commercial batches from synthesis C are available for up to 24 and 18 months, respectively, and a re-a test period of 24 months stored not above 25°C in a very tight packaging can be granted.

Drug Substance (to be changed in the EPAR to "Active Substance") Amlodipine Besilate

Amlodipine besilate (INN) is described in the Ph.Eur and is manufactured by two active substance manufacturers. Both manufacturers have presented Certificates of Suitability (CEP). The three CEPs, current version, are provided in the regional section of the dossier



Amlodipine is a white or almost white powder. Physico-chemical properties such as solubility in various solvents, melting point, polymorphism and chirality have been described. The substance is used as a racemic mixture (R and S isomers). There is no polymorphism of Amlodipine besylate described in the literature.

All the information relating to the manufacturing process, control of materials, critical steps and intermediates, manufacturing development, elucidation of the structure and impurities is covered by the CEP therefore no information was included in the dossier.

Specification

Adequate specification from the active substance suppliers includes the following tests: description, particle size (laser diffraction), appearance of solution, identity (IR, XR, HPLC), assay (HPLC), related substances (HPLC), residual solvents (GC), water content (Karl Fisher), sulfated ash (Ph.Eur.), optical rotation (Ph.Eur.), heavy metals (ICP-OES), microbial contamination.
Upon receipt from the commercial manufacturers, the active substance is tested in accordance with internal Novartis testing monographs specific for each supplier.
The monographs are based on the requirements for amlodipine besilate as found in the Ph. Eur. monograph, and include additional tests needed to conform to Novartis internal standards.
The applicant has put in place additional tests needed by comparison to the Ph.Eur. monograph to ensure the consistency of quality for the active substance between and within each supplier. The specification has been adequately justified and especially limits for impurities, heavy metals, residual solvents have been toxicologically justified.
In addition, amlodipine besilate is controlled for the content in besylate esters that are known to be genotoxic. Moreover, according to the Q&A document on the CHMP Guideline on the Limits of Genotoxic Impurities (EMA/CHMP/SWP/431994/2007) the tolerated amounts of besylate esters should not be cumulated since the benzenesulfonate impurities are structurally related. The limits for besylate esters in amlodipine besylate have been restricted to NMT 75 ppm each and NMT 150 ppm for the sum. This was found acceptable.
In summary, the active substance is controlled according to the requirements of the Ph. Eur. monograph with the addition of the following tests, which are not source specific: identification by XRPD and HPLC, Heavy metals, clarity of solution, colour of solution and microbial limits. Requirements for additional impurities and residual solvents are included in the specifications and are active substance source specific.

All analytical procedures used for testing the active substance have been properly described. Compendial methods are used for clarity and colour of the solution, identification, water content, sulphated ash, optical rotation, related substances and assay.
In-house analytical methods are used for particle size determination, identification, impurities, residual solvents, heavy metals and microbial enumeration test. Non-compendial methods have been validated in line with ICH guidelines.

Nine batches from both active substance manufacturers were tested for compliance against the test monographs. Certificates of analysis showed that all the batches meet the Ph.Eur. test requirements and all additional testing requirements from the applicant. Results demonstrate that the quality of the active pharmaceutical ingredient batches of both suppliers is comparable.

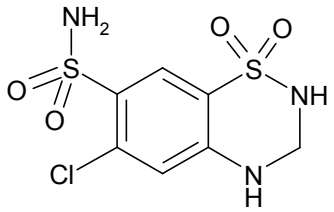
For one manufacturer, the drug substance is filled in clear polyethylene bag, tied in a black polyethylene bag, tied and in HDPE container. For the other manufacturer, it consists of a polyethylene inner bag in a black polyethylene outer bag in or without (Process II) a cardboard box or polypropylene

pail with lid. The certificates of compliance with the Ph.Eur. and the foodstuff legislation for the packaging materials have been provided

Stability
For one manufacturer, a retest period of 5 years and 1 year (depending on the synthetic route) have been granted on the CEPs. For the other manufacturer, the CEP provides no re-test period, long-term and accelerated stability data are provided but the Applicant commits to test each batch of amlodipine besilate before producing the drug product. Testing will be performed until an in-house re-test period is specified.

Drug Substance Hydrochlorothiazide or HCTZ

Hydrochlorothiazide or HCTZ (INN) is a white to almost white powder, controlled according to PhEur monograph. Its chemical structure is represented as follow:



General properties such as solubility in various aqueous and non-aqueous solvents, dissociation constants, distribution coefficients, optical rotation (inactive since does not possess an asymmetric center), water sorption properties (non-hygroscopic) and polymorphism (Form I is the normally isolated crystalline form of the active substance) have been extensively studied.

Manufacture

Both suppliers posses a CEP. Both manufacturers supplying the "crude" HCTZ comply with PhEur requirements.

Commercially available hydrochlorothiazide (or "crude" HCTZ) from both suppliers is further purified by recrystallization and micronised by the applicant. The final HCTZ is tested against the applicant's testing monograph.

Satisfactory control of reagents and solvents has been presented. No critical process steps have been identified and no intermediate product is formed during manufacture of hydrochlorothiazide. No process validation was deemed necessary.

The structure of HCTZ is supported by the synthetic route and has been elucidated by elemental analysis, ultraviolet (UV) and infrared (IR) spectroscopy, proton (^{1}H-NMR) and carbon (^{13}C-NMR) nuclear magnetic resonance. A comprehensive analysis of polymorphism was carried out using X-ray powder diffraction spectra, Raman spectra, DSC curves and thermogravimetry. The analysis showed that forms I and II could be distinguished and differentiated from solvate forms. Form I is the form usually obtained when hydrochlorothiazide is manufactured.

Specification

From the ASMF holder: Specification for hydrochlorothiazide are according to Ph. Eur or stricter. and satisfactory analytical results of five batches are reported including testing of additional residual solvents (in line with ICH requirements).

From the applicant: Micronized hydrochlorothiazide specification including appearance, physico-chemical properties, identification (IR and UV), assay (HPLC and titration), related substances, loss on drying, sulfated ash, heavy metals, microbial contamination fulfills the requirements of the current Ph.

Eur. analytical methods have been satisfactorily described and in-house methods have been validated in accordance with ICH requirements.
Analytical results of six batches of micronized hydrochlorothiazide obtained from the different suppliers were presented and in line with the retained specification. Results confirm batch to batch consistency and uniformity of the quality of the substance and indicate that the process is under control.

The analytical results of three batches of micronized hydrochlorothiazide are presented.
Bulk hydrochlorothiazide is stored in metallic drums lined with two polyethylene bags which are sealed with a plastic closure.
Hydrochlorothiazide is packed in polyethylene bags and wrapped with kraft paper kept in a fiber drum.
Appropriate specification for primary packaging material including identification test by IR, appearance, size and microbiological tests was provided along with certificate of analysis.

Stability

Stability studies have been carried out by the applicant on eight production batches of micronized hydrochlorothiazide under ICH long term storage conditions (up to 5 years, 25°C / 60% RH), accelerated conditions (6 months data, 40°C / 75% RH), stress testing and photostability testing. The quality characteristics (e.g. physical characteristics like clarity and absorbance of the solution in dimethyl sulfoxide, impurity profile and assay) of the active substance are unchanged as demonstrated by comparative analytical data.

Results of data at the long term storage conditions of 25°C / 60% RH up to 5 years and 6 months data at accelerated storage conditions of 40°C / 75% RH were provided. The data support 5 years re-test period for micronized hydrochlorothiazide when protected from light.

2.2.3. Finished Medicinal Product

The aim of the formulation development of Rasitrio film-coated tablet was to obtain an immediate release tablet combination product that would be bioequivalent to the marketed products containing each active substance individually.

The five different tablet strengths with the following aliskiren/amlodipine/hydrochlorothiazide ratios are described as follows:

150/5/12.5 mg: Violet white film coated tablet, ovaloid convex with bevelled edges, with debossing "YIY" on one side and "NVR" on the reverse side of the tablet.
300/5/12.5 mg : Light pink film coated tablet, ovaloid convex with bevelled edges, with debossing "LIL" on one side and "NVR" on the reverse side of the tablet.

300/10/12.5 mg: Light red film coated tablet, ovaloid convex with bevelled edges, with debossing "UIU" on one side and "NVR" on the reverse side of the tablet.
300/5/25 mg: Pale orange brown film coated tablet, ovaloid convex with bevelled edges, with debossing "OIO" on one side and "NVR" on the reverse side of the tablet.

300/10/25 mg: Brown film coated tablet, ovaloid convex with bevelled edges, with debossing with "VIV" on one side and "NVR" on the reverse side of the tablet.

The excipients used for the core tablets are common standard pharmaceutical excipients: microcrystalline cellulose, crospovidone, povidone, magnesium stearate, silica colloidal anhydrous, ethanol with 5% isopropanol.
The Coating premixes (white, yellow and red) are commercially available materials containing iron oxides and/or titanium oxides, macrogol, talc and hypromellose.

There are difference in the ratios of the film-coating pre-mixes that make the various strengths distinguishable.

The component of the premixes are given and comply with the standard of the Ph.Eur. or with the Directive 2008/128/EC. The difference in the premixes is the colourant (iron oxide and titanium dioxide).

The primary packaging consists of tablets are PA/AL/PVC blister packs (Alu blisters) and PCTFE/PVC blister packs backed with a heat sealable lacquered aluminium foil.

Pharmaceutical development

Aliskiren is a single diastereoisomer with 4 S-configured chiral centers. Its hemifumarate salt was selected for the drug product, because it was the only one which showed crystallinity. Aliskiren hemifumarate is a white to slightly yellowish hygroscopic crystalline powder with high solubility and low permeability according to the BCS (class 3). Aliskiren does not possess adequate compactability properties therefore needs granulation. Aliskiren has shown very good chemical compatibility with all the excipients used in the formulation, proved by previously approved formulations. Given the high solubility, particle size is not a concern however the particle size is checked to be under 1000 µm (90%). The crystalline form is checked in the specifications.

Amlodipine besylate is described in the US Pharmacopoeia and Ph.Eur. From the literature it is known to be well absorbed (90% in humans) and with a good solubility. No classification according BCS is given, however given the low dose it may be considered as a high solubility drug. Particle size may be an issue and therefore is controlled by laser diffraction. Amlodipine besylate is sourced from two drug substance suppliers with CEPs.

HCTZ is described in USP and European Pharmacopeia. It is a white to almost white powder and very slightly soluble in water and in acidic medium. Solubility increases at alkaline pH but still remain slightly soluble. Two polymorphic forms of hydrochlorothiazide have been identified: form I and form II. The final crystallization step of current manufacturing process is performed in methanol and water and yields predominately form I. The two forms show similar solubility and intrinsic dissolution rate in physiological media. No impact on bioavailability is foreseen.

The excipients selected are standard ingredients in tablet formulations, and are in compliance with internationally accepted pharmacopoeial standards. The concentrations of each excipient are within the usual range of application.

No specific compatibility studies between the three drug substances are presented and compatibility with excipients is claimed on the basis of previous authorizations. In addition, in this application, adequate compatibility studies between the three active substances and the excipients were performed, along with stability data. The results confirm there is no incompatibility observed.

The tablet cores are coated with a non-functional coating to provide a distinctive tablet colour to identify the different dosage strengths. The basic coating premixes are a combination of ingredients established for use in medicinal products.
The premixes themselves do not appear in any pharmacopoeia; but the ingredients meet compendial requirements and/or international standards.

The development of the combination product was initially based upon the formulation and manufacturing process of the already authorised products Rasilez HCT (aliskiren/HCTZ) and Exforge (valsartan/amlodipine).

Overages
A 20 % overage is included in the film coating suspension to compensate for any losses that may occur during the film-coating process.

Dissolution

Dissolution studies were presented to demonstrate drug release. The methodology selected was based on the methods used for existing marketed products Rasilez and HCT/Rasilez HCT. The method was similar to the USP method for hydrochlorothiazide tablets and amlodipine tablets.
The sink conditions are respected for all actives given the low dosage of amlodipine and hydrochlorthizide. The choice of the medium is acceptable since the method has already been approved for marketed formulations. The discriminative power of the method to distinguish different formulations was demonstrated.

To support biowaivers, dissolution data for the Rasitrio film coated tablet formulations (five dosage strengths, in dissolution media under the same conditions are presented in comparison with the dissolution of the biobatch. Based on the f_2 values the dissolution profiles are considered similar in all media. Based on the above, the Biowaiver can be accepted in line with the Note for Guidance on Bioequivalence.

Based on the available stability data, the following packaging materials are claimed to be sufficiently protective and compatible with the film-coated tablets: PA/AL/PVC blister packs (Alu blisters) and PCTFE/PVC blister packs.

Adventitious agents
There are no excipients of human or animal origin used in the manufacture of the finished product .A declaration that the magnesium stearate used is of vegetable origin is provided.

Manufacture of the product

Details of the manufacturing process and appropriate in-process controls including parameters such as mean mass, individual mass, thickness, hardness, friability, disintegration time have been provided.

The manufacture of the tablets can be summarised as follows and this applies to all five strengths: formation of the aliskiren granulate, formation of the amlodipine/HCTZ granulate, final blending followed by compression and film-coating.

The manufacturing process presents some critical points, especially concerning the homogeneity of blends, due to the low concentration (0.5-2.5%) of amlodipine and HCTZ.

Since both amlodipine and hydrochlorothiazide amlodipine are dosed at very low concentrations, the applicant has discussed the criticality of the blending step. Adequate discussion on the assessment of blending times and conditions has been provided. The blending times are included in the updated flow chart of the manufacturing process.

A summary of the process validation scheme is available in section 3.2.R. The sampling plan contains the sampling points, tests, sample quantities and acceptance criteria for final blend, compression and film-coated tablets. Since the manufacturing process is not considered standard (due to the low content of two of the active substances) validation results for three full scale batches of each strength have been required preapproval. The validation data submitted show that the manufacturing process is robust and consistently yields drug product, which meets the predetermined quality characteristics.

Control of Excipients

All the excipients used in the core formulation comply with the quality requirements of the applicable compendial monograph.
Monographs for the premixes themselves do not appear in any pharmacopoeia, however, their respective ingredients meet compendial requirements and international standards. These include, Macrogol/PEG 4000 (Ph. Eur.), Talc (Ph. Eur.), Hypromellose (Ph. Eur.), Titanium dioxide (Ph. Eur.) and iron oxides (red, yellow) controlled according to commission directive 2008/128/EC and the NF.

Certificates of analysis for all pharmacopoeia excipients have been provided. Satisfactory in-house specifications and certificates of analysis are provided for the coating. Satisfactory method validation data has also been provided where applicable.
In addition, where relevant, additional testing has been carried out (functionality test and residual solvents in line with ICH requirements).

Specifications

Adequate specification at release and at the end of shelf-life for all five strengths of the finished product includes: appearance (visual examination), identification of aliskiren amlodipine and HCTZ (UV and and HPLC), identification of colorants (colour reaction), dissolution (HPLC), degradation products of all three actives (HPLC), accompanying substances (besylate esters, HPLC), water content (Karl-Fisher), assay for active substances (HPLC), uniformity of dosage units (Ph. Eur), and microbial limit tests (Ph Eur),

residual solvents (GC) - The specification for the drug product is considered acceptable and the limits for the degradation products are justified based on stability data and do not raise any concern from a toxicological point of view.

Analytical methods have been adequately described and validated in accordance with the ICH guidelines Q2R1.

Batch analytical data

Batch results have been provided for at least 3 pilot batches per strength, the results were found in compliance with the specification and confirm the consistency of the process and the performance of the analytical testing.

Container closure system

The primary packaging for the film-coated tablets are PA/AL/PVC blister packs (Alu/Alu) and PCTFE/PVC blister packs backed with a heat sealable lacquered aluminium foil. Testing Monographs for PA/AL/PVC forming foil, for PCTFE/PVC forming foil and for Aluminium lidding foil are presented.

The components of the PA/AL/PVC and PCTFE/PVC blisters are tested for cleanliness, total thickness and identity (IR). In addition the Applicant states that the packaging components comply with Ph. Eur. requirements (where applicable, e.g. PVC, PA) and/or foodstuff legislation.

Stability of the product

Stability results have been presented 15 pilot batches (three batches per strength) kept in the commercial packaging.

The batches have been stored under ICH long term testing at 25°C/60%RH and intermediate testing 30°C/65%RH (12 months), accelerated testing at 40°C/75%RH (6 months), as well as other temperatures (e.g. - 20°C, 5°C and 50°C). Special tests (e.g. photostability and microbial enumeration) have also been performed.

The characteristics tested during the stability study were: appearance, water content, besylate esters, dissolution (all actives), assay and degradation products (all actives), microbial limits.

Parameters remained within the specification when the product was kept at 25°C and 30°C and no significant change could be observed, slight increase was observed under accelerated conditions but all results remained within the specification. Photostability data showed that the product is stable in the proposed packages.

Stability data support the proposed shelf life under the precautions of storage described in the Product Information.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance aliskiren hemifumarate is optically active with four chiral carbons but exists as a single diastereoisomer. It is manufactured via 2 stereochemically controlled syntheses (route B and route C). Controls of stereochemistry, polymorphism and impurities have been fully discussed. Appropriate specification has been presented. Stability studies conducted according to the ICH guidelines showed that aliskiren hemifumarate is stable. Based on the discussion above, the data support synthesis B support a retest period of 30 months stored not above 25°C in a very tight packaging. Stability data on pilot and commercial batches from synthesis C are available for up to 24 and 18 months, respectively, and a re-a test period of 24 months stored not above 25°C in a very tight packaging can be granted.

The active substance amlodipine besilate is covered by Certificates of Suitability CEP from 2 suppliers. Adequate specification has been presented. For one manufacturer, a retest period of 5 years and 1 year (depending on the synthetic route) have been granted on the CEPs. For the other manufacturer,

the CEP provides no re-test period. Long-term and accelerated stability data are provided but the Applicant commits to test each batch of amlodipine besilate before to produce the drug product.

The active substance Hydrochlorothiazide or HCTZ (INN) is covered by Certificate of Suitability CEP and ASMF procedure. The last steps of crystallisation and micronisation are performed by the applicant. Adequate specification has been presented. Results of data at the long term storage conditions of 25°C / 60% RH up to 5 years and 6 months data at accelerated storage conditions of 40°C / 75% RH were provided. The data support a 5 years re-test period for micronized hydrochlorothiazide when protected from light.

Rasitrio film-coated tablets are formulated as an immediate release formulation with well-known excipients. Compatibility with regard to excipients is justified by stability results. The pharmaceutical development is comprehensive and adequate. Manufacturing method has been described and allows the production of a consistent and homogeneous product. The manufacturing process is not a standard one, since two of the actives are present in very low concentrations (ranging from 0.5 to 2.5% approx) and the applicant has presented an adequate validation protocol as well as validation results for three full scale batches of each strength. The validation data submitted show that the manufacturing process is robust and consistently yields drug product, which meets the predetermined quality characteristics.
The description and choice of the container is acceptable based on stability data. Drug product specification is satisfactory and in line with ICH guidelines. Stability results have been presented on 3 pilot batches for each strength in two different packaging configurations (PA/Al/PVC (Alu) blister packs and in PCTFE/PVC blisters).
Stability data support the proposed shelf life under the precautions of storage described in the Product Information.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this medicinal product is considered satisfactory when used with the conditions defined in the SPC. The documentation provided for the active substances aliskiren hemifumarate, amlodipine besilate and HCTZ is comprehensive and adequately detailed. The pharmaceutical development is adequate and took into consideration the properties and the stability of the three active substances. The excipients used are common excipients for immediate release dosage forms. Similarly, the packaging material is well documented and no incompatibility has been noticed. The validation of the manufacturing process ensures consistency and reproducibility of the finished product. The finished product has been satisfactorily controlled and stability studies conducted under ICH conditions showed that the product is stable throughout the proposed shelf-life.

2.2.6. Recommendation(s) for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

No preclinical pharmacodynamic studies were conducted with Rasitrio. The available evidence from literature, concerning the single components, was submitted. The lack of preclinical pharmacology data is justified by the lack of adequate animal models. This is considered acceptable. No specific safety or pharmacodynamic drug interaction studies were conducted and reference is made to the evidence concerning single components. The pharmacokinetics and metabolism of the individual components of SAH100, aliskiren, amlodipine and hydrochlorothiazide, have been characterized and studied preclinically as well as clinically. No preclinical pharmacokinetic studies have been performed with Rasitrio.
With respect to the toxicological studies, extensive preclinical safety studies were conducted in mice, rats, and marmosets during the development of the aliskiren, amlodipine and hydrochlorothiazide monotherapies. General toxicity studies in rats with durations up to 13 weeks were also conducted with the combination of aliskiren and hydrochlorothiazide as well as the combination of aliskiren and amlodipine. There were no new toxicities identified from these toxicity studies. In view of considerable preclinical and clinical safety data, it was not deemed necessary to conduct preclinical toxicity studies with Rasitrio.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Studies on pharmacodynamics for were not conducted primarily due to the lack of appropriate animal models. The testing of human renin inhibitors in experimental animals is significantly hampered by the species specificity exhibited by renin and the human renin inhibitor, aliskiren, has relatively weak potency against rat renin, and consequently shows poor efficacy in this species. Due to the lack of appropriate animal models, pharmacology results for the FDC were not generated.

Secondary pharmacodynamic studies

No specific preclinical secondary pharmacodynamic studies were conducted with Rasitrio, due to the lack of appropriate animal models as described above.

Safety pharmacology programme

There were no safety pharmacology concerns with the individual components of Rasitrio and therefore, further investigations were not conducted for the fixed combination of aliskiren/amlodipine/hydrochlorothiazide, which is consistent with the recommendations of the CHMP guidance EMEA/CHMP/SWP/258498/2005.

Pharmacodynamic drug interactions

The safety of aliskiren, amlodipine, and hydrochlorothiazide has been demonstrated in preclinical studies, clinical trials and post-marketing programmes. Given the distinct mechanism of action of aliskiren, amlodipine, and hydrochlorothiazide, the combination of these drugs is not expected to be of concerns with respect to drug-drug interactions.

2.3.3. Pharmacokinetics

Aliskiren, amlodipine and hydrochlorothiazide are approved and marketed products in both, the EU and USA. The pharmacokinetics and metabolism of the individual components (aliskiren, amlodipine and hydrochlorothiazide) are well characterised and have been extensively studied preclinically as well as clinically. The pharmacokinetic profiles of the single components of Rasitrio have been reviewed and data for the combinations aliskiren/amlodipine and aliskiren/hydrochlorothiazide are also reported. There are a number of preclinical studies described in the literature. Special non-clinical pharmacokinetic and metabolism studies were not performed with Rasitrio. The individual components are not anticipated to behave or act differently when combined. No specific studies with the FDC were conducted on distribution, placental passage or concentration in milk as based on the behaviour of the monocomponents, these were deemed unnecessary. The metabolic and excretion pathways of aliskiren, amlodipine and hydrochlorothiazide were briefly reported and do not indicate the need for specific studies with the FDC. The different clearance mechanisms of the individual components (i.e. hydrochlorothiazide: renal clearance, amlodipine: metabolism clearance and aliskiren: biliary clearance) do not suggest an obvious potential interference on the disposition of the components when administered in a combined manner. In addition, preclinical as well as clinical evidence for the monotherapies suggests a low drug-drug interaction potential at the biochemical level of transporters and P450 inhibition. Thus, a clinically significant drug-drug interaction on the basis of inhibition is also not likely for Rasitrio.

A brief overview of the pharmacokinetic properties of the individual monocomponents as derived from the submitted data based on literature recherché is described below.

Absorption
The rate of absorption of aliskiren was rapid in mice, rats, and moderate in dogs and marmosets. Aliskiren has very a low bioavailability (1%-3%) in all studied species but dogs. After oral dosing, the concentration-time profiles of aliskiren (and total radioactivity with administration of radiolabelled compound) were highly variable and peaked between 0.25 and 3 hours in all species investigated. Hydrochlorothiazide is well absorbed in all tested animal species and is largely excreted in unchanged form with urine. Oral doses of amlodipine were well absorbed in mice, rats and dogs.

Distribution
The volume of distribution (Vss) of aliskiren at steady-state was high in the rat, moderate in humans and mice, and low in marmosets. Binding of aliskiren to plasma proteins was moderate with free fractions (fu) of 29% (mouse), 38% (rat) and 50% (human). Amlodipine was highly distributed into tissues with a large volume of distribution around 21-32 L/kg across various tested species. Amlodipine was highly bound to human plasma proteins (98% at a drug concentration of 50 ng/mL). Protein binding was similar in dogs and rats (97% and 94% respectively). Hydrochlorothiazide binds to plasma proteins only to a low extent and is moderately distributed in body tissue with a volume of distribution following oral administration corresponding to 0.83 L/kg.

Metabolism
Aliskiren was metabolised to a low to moderate extent in humans, marmosets, rats and mice (about 15% to 25% of dose). The most abundant component in plasma and excreta was unchanged aliskiren. Primary metabolic pathways involved oxidative reactions on the phenol moiety of aliskiren, like O-dealkylation, and further oxidation to the carboxylic acid leading to metabolites M1 to M4. These oxidation processes had been found to be catalyzed largely by CYP3A4/5 enzymes. Minor metabolic pathways were the formation of glucuronide metabolites (M5 and M6) and hydrolytic cleavage of aliskiren at the amide bond leading to M10 and/or M11. All metabolites observed in plasma were also found in the excreta either in free or conjugated form. Amlodipine was eliminated mainly through extensive, though slow metabolism and with low first pass extraction in mouse, dog and humans. The metabolites showed negligible calcium channel antagonist activity relative to amlodipine. Only a small fraction of the dose (up to 5%) was recovered in urine as unchanged drug. Hydrochlorothiazide is not metabolized to a relevant degree and the bulk of the dose (95% of dose) is excreted unchanged in urine.

Excretion
In mice, rats, marmosets and humans, aliskiren and its metabolites were predominantly excreted into faeces (≥88% of the absorbed oral dose), indicating high biliary/faecal elimination of the absorbed fraction of the administered dose. Renal excretion was generally low in all investigated species (≤4.5%, p.o. and ≤15%, i.v.), including humans. Excretion was complete within 7 days, with the main fraction of a radioactive dose recovered within 24-48 hours. About 50% of an oral dose of amlodipine was recovered in urine and feces of rats and dogs and orally administered hydrochlorothiazide is excreted largely unchanged with urine. In humans, >95% of the absorbed hydrochlorothiazide was excreted in urine.

Pharmacokinetic drug-drug interactions
Interactions on a pharmacokinetic basis, in terms of enzyme induction, inhibition or substrate, as well as protein binding, were reviewed for the single components of Rasitrio. The different clearance mechanisms of the individual components of Rasitrio (i.e. hydrochlorothiazide: renal clearance, amlodipine: metabolism clearance, aliskiren: biliary clearance) do not suggest an obvious potential interference on the disposition of the components when administered in combination. In addition, preclinical as well as clinical evidence for the monotherapies suggests a low drug-drug interaction potential at the biochemical level of transporters and P450 inhibition manner. Thus, a drug-drug interaction on the basis of inhibition is not likely for the triple combination of Rasitrio. Therefore, additional non-clinical studies on the interaction potential of the triple combination were not deemed necessary.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies were fully evaluated for aliskiren, amlodipine and hydrochlorothiazide as part of their mono-therapy development programs. The findings from these studies were generally consistent with those anticipated for the drugs affecting the renin-angiotensin system; further single dose toxicity studies were therefore not conducted

Repeat dose toxicity

Repeat dose toxicity studies were conducted for aliskiren, amlodipine and hydrochlorothiazide, as well as for the combinations of aliskiren and amlodipine, aliskiren and hydrochlorothiazide. The toxicity findings from these studies were generally consistent with those of each component from the previously conducted toxicity studies. There were no new toxicity findings or more severe toxicities noted from the treatment of the combinations in durations up to 13 weeks. In view of the considerable safety data available for each component of Rasitrio and the approved double combinations, it is expected that safety profile of Rasitrio is similar to those of the double combinations. Therefore, no additional repeated dose toxicity studies were conducted.

Aliskiren
Aliskiren was evaluated for general toxicity in rats and marmosets. Premature deaths were encountered at doses ≥ 200 mg/kg/day in oral (gavage) repeated dose toxicity study in rats. As aliskiren is a local irritant and can cause necrosis of the respiratory epithelium, the deaths were attributed to aspiration of the dosing solution into the respiratory tract rather than systemic toxic effects. In marmosets, two incidences of urinary stasis in decedent animals were attributed to hypotension and poor renal perfusion. Other changes in marmosets included reductions in erythropoietic parameters probably due to the effect of the renin-angiotensin system on the production of erythropoietin in the kidney. Similar findings have been previously observed with a variety of inhibitors of the renin-angiotensin system. Arteriolar or juxtaglomerular hypertrophy/hyperplasia were also recorded in the kidneys and were considered to be due to the hypertrophy/proliferation of the renin secreting periarteriolar cells of the juxtaglomerular apparatus. These changes were not accompanied by adverse effects on the renal vasculature or the urinary system and they were regarded as exaggerated pharmacological effects.

Amlodipine
Amlodipine was evaluated for toxicity in mice, rats and dogs, in which higher doses of amlodipine resulted in compound-related effects with little relevance to humans at clinical doses. In the acute toxicity studies, amlodipine caused severe peripheral vasodilation and hypotension in dogs, and caused mortality in mice and rats. In oral subacute/chronic toxicity studies in rats, there was thickening of the adrenal zona glomerulosa, hepatotoxicity, decreases in body weight, and decreases in plasma sodium, chloride and calcium and increases in plasma urea. In oral subacute/chronic toxicity studies in dogs, treatment-related effects included diuresis, increases in heart rate and lesions in the gingiva and the wall of right atrium.

Hydrochlorothiazide
Toxicity studies with hydrochlorothiazide were conducted in mice and rats by dietary administration for 15-days, 13-weeks and 2-years. No rats died during the 15-day or 13-week studies at dietary concentrations of up to 50,000 ppm. Increased nephrosis and mineralisation at the renal corticomedullary junction were the primary toxic effects in rats. Deaths of male mice in the high-dose group in the 13-week study were likely to be related to compound administration and resulted from nephrosis, calculi, inflammation and epithelial hyperplasia in the urinary bladder.

Aliskiren/amlodipine
The nonclinical safety profile of aliskiren/amlodipine was evaluated in general toxicity studies in 2- and 13-week oral (gavage) toxicity studies in rats. The 2-week rat study was a dose range-finding toxicity study. The toxicity findings in this study included those in large intestine at doses of 100/3 and 300/10 mg/kg/day, and characterised as inflammation and hypertrophy/hyperplasia. The changes are consistent with those previously observed for aliskiren in repeated-dose toxicity study in rats. In the 13-week rat study with aliskiren/amlodipine, the adverse effects were mainly in the high dose group of the combination (300/10 mg/kg/day), aliskiren or amlodipine alone groups. The findings included premature deaths and clinical signs of shallow/deep/laboured breathing, abnormal breathing sounds and salivation. The findings were consistent with those observed in the previous 13-week rat study with aliskiren and associated with local irritation of aliskiren as a result of aspiration of the dosing solution into the respiratory tract rather than systemic toxic effects. Minimal changes were noted in clinical pathology parameters, including decreases in mean lymphocyte counts and decreases in globulin concentrations in the combination group and the amlodipine alone group. The pathological findings included pale discoloration or foci of the adrenals and corresponding histopathological changes of minimal hypertrophy/vacuolation of the zona glomerulosa in rats treated with amlodipine at 10 mg/kg/day and SPA100 at 300/10 mg/kg/day.

Aliskiren/hydrochlorothiazide
Preclinical safety studies conducted with SPH100 included 2- and 13-week oral (gavage) repeated dose toxicity studies in rats. In the 2-week rat study, the dose of 300/25 mg/kg/day (aliskiren and hydrochlorothiazide) resulted in morbidity and an early group sacrifice. Increased plasma urea and creatinine concentrations and basophilic tubules, hyaline casts and tubular necrosis in the kidney were frequently observed and suggest that the moribund condition of the animals was attributed to marked hypotension and poor renal perfusion associated with exaggerated pharmacological effect of the combination. In the 13-week rat study, the toxicity findings included mild effects on the kidneys and adrenal glands at doses up to 150/12 mg/kg/day (aliskiren and hydrochlorothiazide) that were consistent with the pharmacological effects of aliskiren and/or hydrochlorothiazide. Alterations in kidney function were seen at all doses of the combination and with aliskiren or hydrochlorothiazide treatment alone and comprised reversible decreases in serum potassium and chloride concentrations and increased urine volume but there were no corresponding histopathological alterations. Minimally increased cellular vacuolation in the zona glomerulosa was observed in the adrenal glands of animals treated with hydrochlorothiazide alone and among all groups treated with aliskiren/hydrochlorothiazide. These alterations persisted on completion of the 4-week recovery period for animals treated at the highest dose of the combination. No changes were observed in the gastrointestinal tract of these animals. In conclusion, aliskiren/hydrochlorothiazide was generally well tolerated by rats and the findings observed in the toxicity studies were clearly attributable to the exaggerated pharmacological effects of aliskiren and/or hydrochlorothiazide.

Genotoxicity

No genotoxic potential was identified for aliskiren or amlodipine. Genotoxicity studies conducted with hydrochlorothiazide included: Salmonella (Ames test), chromosomal aberration (in vitro cytogenetics), drosophila (sex-linked recessive lethal/reciprocal translocation), mouse lymphoma assay and sister chromatid exchange assay (in vitro cytogenetics). Mouse lymphoma assay and sister chromatid exchange assay had positive results, whilst the other tests were negative. Based on all the available literature, the *in vivo* genotoxic potential of hydrochlorothiazide is low. Since the genotoxic potential of alikiren, amlodipine and hydrochlorothiazide was fully evaluated individually, no additional genetic toxicity tests were performed for the triple combination.

Carcinogenicity

Carcinogenic potential of aliskiren, amlodipine and hydrochlorothiazide was fully evaluated individually and no carcinogenic potential was identified for either substance. No additional carcinogenicity studies were performed for the triple combination.

Reproduction Toxicity

Reproduction and developmental toxicity for aliskiren, amlodipine and hydrochlorothiazide were fully evaluated individually. There were no reproductive and/or developmental toxicity noted with aliskiren in rats and rabbits and with hydrochlorothiazide in rats and mice. Amlodipine was not teratogenic, however prolonged the duration of gestation and labour in rats, decreased the litter size and increased the number of intrauterine deaths at 10 mg/kg/day, which is likely to be connected with exaggerated pharmacological effect. In view of the existing data for aliskiren, amlodipine and hydrochlorothiazide, it is considered that additional reproductive and developmental toxicity studies with Rasitrio were not necessary.

Toxicokinetic data

The toxicokinetic analyses were included in the evaluation of repeat toxicity studies for the individual components and/or the double combinations and no safety signals have been identified.

Local Tolerance

No specific local tolerance studies were conducted with Rasitrio since local tolerance *via* the intended clinical route administration (oral) was assessed during the repeat dose toxicity studies in rats for each mono-therapy and for the approved double combinations. No concerns were identified.

Other toxicity studies

The available nonclinical safety data for aliskiren, amlodipine and hydrochlorothiazide do not indicate any potential for antigenicity, immunotoxicity or dependency. In view of these data and the available clinical experience with each of the mono-therapy components, further nonclinical studies to evaluate these effects for SAH100 are not considered necessary in accordance with the CHMP guideline EMEA/CHMP/SWP/258498/2005.

2.3.5. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) submitted for Rasitrio was prepared in compliance with the CHMP guideline EMEA/CHMP/SWP/4447/00. The active molecules have been assessed separately. Predicted environmental concentrations exceeded the threshold value of 0.01 µL and triggering a Phase II – Tier A for all three active pharmaceutical ingredients.

Aliskiren shows low acute and chronic toxicity towards aquatic organisms. Based on the low adsorption coefficient determined for sludge, partitioning to soil is not expected for aliskiren. Bioaccumulation is not expected. The value of log Koc < 4 in the adsorption/desorption study suggests a low to moderate sorption to soil and sludge. Due to the absence of UV absorption above 290 nm, photodegradation is expected to be minimal. Aliskiren has no significant potential to inhibit the microbial activity of activated sludge, even at high concentrations, and is not readily biodegradable. The assessment of transformation in aerobic water sediment systems showed values that exceed the trigger level for a Tier B sediment assessment of 10 % of drug substance in sediment after 14 days. Although a highly conservative approach in predicted environmental concentrations (PEC) calculation has been adopted, the PEC_{water} /$PNEC_{surfacewater}$, $PEC_{microorg}$ /$PNEC_{microorg}$, $PEC_{groundwater}$ /$PNEC_{groundwater}$ values are well below the recommended threshold values indicated in the regulatory guidelines. Results of Tier B risk assessment on sediment dwelling organisms, in particular on the midge larvae *Chironomus riparius*, suggests that no risk for the sediment compartment due to exposure to aliskiren is expected. Considering the recent evaluation of SVP100 (aliskiren/valsartan) and SPA100 (aliskiren/amlodipine) and the evidences provided, the ERA on aliskiren can be considered in compliance with EMA guidelines.

Amlodipine shows significant chronic toxicity to aquatic species with the green algae species *Pseudokirchneriella subcapitata* being the most sensitive species tested. Amlodipine has the potential to inhibit the microbial activity of activated sludge at concentrations higher than 10 mg/L. However, amlodipine is neither considered to be stable in surface water, based on its photolability, nor is it persistent in sediment compartments. Although a highly conservative approach in PEC calculation has been adopted, the PEC_{water} /$PNEC_{surfacewater}$, $PEC_{microorg}$ /$PNEC_{microorg}$, $PEC_{groundwater}$ /$PNEC_{groundwater}$ values are below the recommended threshold values indicated in the regulatory guidelines. Amlodipine is not expected to bio-accumulate. Nevertheless, clarifications were requested by the CHMP on the degree of

adsorption to sludge and partitioning into sediments, and on the types of sludge tested for amlodipine. These issues were clarified and it was agreed that amlodipine exhibits moderate sorption to sludge and even if the testing protocol did not entirely adhere to the OECD 106 guideline, the moderate Koc values found for amlodipine make significant increases of adsorption in different sludge types unlikely. On the other hand, according to the results of the Transformation in Aquatic Sediment Systems test, more than 10% of the test substance is present in the sediment after 14 days, which triggers a Tier B risk assessment on sediment dwelling organisms. According to OECD 308 guideline, metabolites with concentration >10% in total system water/sediment are to be identified, thus the CHMP recommended that Tier B risk assessment on amlodipine (toxicity to sediment-dwelling organisms OECD218) is provided.

Hydrochlorothiazide shows low chronic toxicity to aquatic organisms. It has no significant potential to inhibit the microbial activity of activated sludge and is not readily biodegradable. No significant adsorption on sludge has been observed and therefore the potential to partition into terrestrial compartments via the potential spreading of STP sludge on agricultural soils is considered to be negligible. The study on transformation in water/sediment systems revealed significant partitioning of hydrochlorothiazide into sediments, thus indicating the need for a sediment risk assessment. After 14 days, 17 % and 24 % of the dose applied to the water/sediment systems were present as extractable parent hydrochlorothiazide in the sediment phase of the low organic carbon and high organic carbon sediment, respectively. Consequently, a toxicity study with the sediment-dwelling larvae of *Chironomus riparius* was conducted and a sediment risk assessment is described in Tier B. Hydrochlorothiazide is not expected to bio-accumulate. The highest risk ratio has been found for sewage treatment plants. Hydrochlothiazide has been found to be non-toxic to the sediment-dwelling larvae of *C. riparius* up to a limit concentration of 10 mg/kg, no risk to the sediment compartment is expected.

Summary of main study results - ALISKIREN

Substance (INN/Invented Name): Aliskiren hemifumarate					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	Faller 2010	Log P = 2.7, Log D = 0.9			Potential PBT: N
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	Below 4.5			not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability	Not readily biodegradable, 5 % in 28 days			P
Toxicity	NOEC or CMR	10 mg/L			not T
PBT-statement :					
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)					> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 1228.4 – 1545.3 cm3/g			
Ready Biodegradability Test	OECD 301B	5 % in 28 days			Not biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, whole\ system}$ = 75-107 days			Tier B sediment Assessment necessary
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	100	mg/L	*Scenedesmus subspicatus*
Daphnia sp. Reproduction Test	OECD 211	NOEC	10	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	10.6	mg/L	*Pimephales promenas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	4470	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism	OECD 219	NOEC	100	mg/L	*Chironomus riparius*

Summary of main study results - AMLODIPINE

Substance (INN/Invented Name): Amlodipine besylate					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	Log Pow = -0.056			Potential PBT: N
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	Below 4.5			not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability	Not readily biodegradable			P
Toxicity	NOEC or CMR	0.029 mg/L			not T
PBT-statement :					
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)					> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	*KF,om sludge = 814 – 1157cm3/g*			
Ready Biodegradability Test	OECD 301B	Not biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ whole\ system}$ = 1.7-4.6 days $DT_{50\ sediment}$ = 3.1 – 16 days			Tier B sediment Assessment necessary
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	0.029	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.22	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	2.2	mg/L	*Pimephales promenas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	10	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism	OECD 219	NOEC		mg/L	

Summary of main study results - HYDROCHLOROTHIAZIDE

Substance (INN/Invented Name): Hydrochlorothiazide					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	Log P = 0.09			Potential PBT: N
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	Below 4.5			not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability	Not readily biodegradable, 37 %			P
Toxicity	NOEC or CMR	10 mg/L			not T
PBT-statement :					
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)					> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$KF_{,oc}^{ads}$ = 28.9 - 33.0 cm^3/g			
Ready Biodegradability Test	OECD 301B	37 %			Not biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50 (water) = 23.0 – 28-2 days DT50 (sediment) = 42.8 – 55.5 days DT50 (total system) = 34.5 – 37.3			Tier B sediment Assessment necessary
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	100	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	100	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	10	mg/L	*Pimephales promenas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	100	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism	OECD 218	NOEC	10	mg/Kg	*Chironomus riparius*

2.3.6. Discussion on non-clinical aspects

No specific studies with Rasitrio were conducted concerning primary and secondary pharmacodynamics, safety pharmacology, animal pharmacokinetics, single-dose toxicity, genotoxic potential, carcinogenic potential, reproductive and developmental toxicity and special toxicity studies. For all of the above aspects, reference was made to previous studies conducted with the single components aliskiren, amlodipine and hydrochlorothiazide, assuming that the individual components of the fixed association were not expected to behave differently when given in combination. As far as pharmacodynamics was concerned, the lack of special studies was also justified by the unavailability of appropriate animal models. The effort to reduce to a minimum the number of experimental animals –taking into account the indications of the EMEA/CHMP/SWP/258498/2005 guideline- is considered acceptable.
After the initial marketing authorization of the anti-hypertensive agent aliskiren, several fixed associations -including aliskiren as a component- have been developed, namely the associations between aliskiren and hydrochlorothiazide, valsartan or amlodipine. These were supported by non-clinical development including 2-weeks and 13-weeks toxicity studies in rats. In addition, there is some

clinical experience available to date with the use of these combinations in practice. Thus, the currently provided literature recherché is considered acceptable by the CHMP.
The CHMP, however, raise a concern on the Environmental Risk Assessment and in the context of technical and scientific progress, recommended that the applicant provides the Tier B assessment on amlodipine (toxicity to sediment-dwelling organisms OECD218) and conducts a shortened version of the OECD308 study to allow for identification of Metabolite 1.

2.3.7. Conclusion on the non-clinical aspects

No specific studies with the fixed combination Rasitrio were conducted concerning primary and secondary pharmacodynamics, safety pharmacology, animal pharmacokinetics, single-dose toxicity, genotoxic potential, carcinogenic potential, reproductive and developmental toxicity and special toxicity studies. Justification for the lack of non-clinical testing has been provided along with the literature overviews available for the mono-components and/or double combinations. This is considered acceptable and in line with the current CHMP guidelines. The environmental toxicity profile of amlodipine should be better characterised and the CHMP recommended conduct of additional testing.

2.4. Clinical aspects

2.4.1. Introduction

The marketing authorisation application is made for the fixed combination of aliskiren/amlodipine/hydrochlorothiazide (Rasitrio) in doses of 150 mg/5 mg/12.5 mg, 300 mg/5 mg/12.5 mg, 300 mg/5 mg/25 mg, 300 mg/10 mg/12.5 mg, and 300 mg/10 mg/25 mg for the treatment of hypertension.

The original application claims the following indication:

> *Treatment of essential hypertension in adults.*
>
> *Rasitrio is indicated as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide, taken either as three single-component formulations or as a dual-component and a single-component formulation, given concurrently, at the same dose level as in the combination.*

Indication granted by the CHMP:

> *Rasitrio is indicated for the treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently at the same dose level as in the combination.*

The regulatory requirements relevant for fixed dose antihypertensive drug combinations are described in the following regulatory guidance documents that have been taken into account during the assessment of this marketing authorization application:

- CPMP/EWP/560/95: NOTE FOR GUIDANCE ON THE INVESTIGATION OF DRUG INTERACTIONS
- CPMP/EWP/238/95 rev2, rev3: NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICAL PRODUCTS IN THE TREATMENT OF HYPERTENSION
- CHMP/EWP/191583/2005: QUESTIONS AND ANSWERS DOCUMENT ON THE CLINICAL DEVELOPMENT OF FIXED COMBINATIONS OF DRUGS BELONGING TO DIFFERENT THERAPEUTICAL CLASSES IN THE FIELD OF CARDIOVASCULAR TREATMENT AND PREVENTION
- CPMP/EWP/QWP/1401/98 rev1/ Corr**: NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOEQUIVALENCE
- CHMP/EWP/240/95 rev1: GUIDELINE OF THE CLINICAL DEVELOPMENT OF FIXED COMBINATION MEDICINAL PRODUCTS

Guidance on the clinical development programme from the CHMP was not sought.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.
In the context of the assessment of the application of Rasitrio, the CHMP requested a GCP inspection of the clinical study SAH2302 (pivotal efficacy study for Rasitrio application) to be performed at one clinical investigator site in Latvia, and in two in Canada.

The GCP inspection raised a number of issues which might have an impact on the assessment of the efficacy of Rasitrio. The most relevant are listed below:

- A large number of aberrant BP readings, which have not resulted in repeat measurements.
- Failure to ensure standardised conditions during BP measurements.
- Too few or too many readings were done for many patients, without any documentation to explain why and with no explanation why specific data were chosen and not others.
- The interval between readings was usually 1 min or less, thus disregarding CHMP instruction.
- A substantial amount of the deviations concerning primary efficacy parameters were not discovered by the clinical research associate (CRA) and consequently did not result in corrective actions.

Due to the lack of focus from the sponsor on the primary efficacy parameter including lack of appropriate quality control (monitoring), it was suspected that the issues relating to the primary efficacy parameter are global in nature and other sites are likely to reveal the same kind of deviations.

For the sake of completeness, it should be noted that, as study SAH2302 was also part of the application for Rasilamlo double combination (aliskiren/amlodipine). As concerns the current application, the CHMP required discussion on the following issue: reliability of the method used for the measurement of the BP. It is of paramount significance due to the fact that all primary and secondary endpoints are based on or are deducted from two variables, that precise measurements of the SBP and DBP are performed. In response to the CHMP question, all inspection findings were addressed. The issues regarding the assessment of efficacy were discussed and further analysis of data were provided. The following claim was put forward by the applicant:

- The presence of aberrant readings (SBP variation ≥ 10 mmHg) in the eCRF for some patients was not necessarily an indication that the protocol was not observed.
- The percentages of patients with aberrant readings were uniformly distributed in all treatment groups, which indicates that if there were any effects of the aberrant readings on the efficacy data, this effect would have been equally balanced in all groups;

Additional analyses were performed by comparing the Full Analysis Set (FAS) vs. patients with and without aberrant readings. The analysis of the change of msSDP and msDBP from baseline to end of study, showed similar results in all groups (with or without aberrant readings). On the basis of these results, it was assumed that the triple combination of aliskiren/amlodipine/hydrochlorothiazide, in both patient groups, with and without aberrant values, is still superior to the corresponding double combinations as previously demonstrated. The CHMP noted that data with exclusion of aberrant BP readings were reported without statistical analysis in subgroups without aberrant readings. Thus, further re-analysis was presented and the results stratified by the following age groups: <65 years, ≥65 years-<75 years and ≥75 years. Such statistical analysis of the treatment-induced BP lowering effect for all study groups after the exclusion of aberrant readings was submitted and the results of this additional analysis are discussed in section on Clinical Efficacy.

- Tabular overview of clinical studies

The original clinical development program supporting the registration of the fixed combination of Rasitrio in the treatment of hypertension consists of a pivotal efficacy and safety Study SAH2302, a long-term efficacy and safety Study SAH2301 and four supportive studies in patients whose blood pressure was not controlled by aliskiren/hydrochlorothiazide double combination Study SPP2344, Study SPP2411, and Study SPP2360 and in patients whose blood pressure was not controlled by aliskiren/amlodipine double combination Study SPA2301. All studies were multicenter with the majority

being multinational. Overall, the initial clinical program included a total of 3910 hypertensive patients, of which 1155 patients received at least 1 dose of any aliskiren/amlodipine/hydrochlorothiazide combination: 568 patients received aliskiren/amlodipine/hydrochlorothiazide combination for at least 180 days (6 months) and 182 patients received the combination for at least 360 days (1 year). Further supportive results were submitted from 4 additional clinical trials, Study SPA2307, Study SPAUS02, Study SPADE01, and Study SPHDE01. An overview of studies, their purpose and other sources of data used are provided in the table below.

Topic Purpose	Details
Dose selection study	**None**
Pivotal efficacy study	
Pivotal short-term, active-controlled study	**Study SAH2302:** double-blind, 8-week, active-controlled, 4-group, parallel study evaluating the triple combination of aliskiren/amlodipine/HCTZ in comparison to dual combinations of aliskiren/amlodipine, aliskiren/HCTZ, or amlodipine/HCTZ
Key long-term efficacy and safety study	
Long-term efficacy and safety study	**Study SAH2301:** open-label, 28 to 54-week study evaluating the long-term safety and efficacy of the aliskiren/amlodipine/HCTZ triple combination
Other studies[1]	
Studies with the use of Aliskiren/amlodipine/HCTZ in patients whose BP was not controlled by aliskiren/HCTZ	
Long-term active-controlled study	**Study SPP2344:** double-blind, 36-week, active-controlled study evaluating aliskiren-based regimen (with optional add-on of HCTZ and amlodipine) in comparison to ramipril-based regimen (with optional add-on of HCTZ and amlodipine) in elderly hypertensive patients
Short-term active-controlled study	**Study SPP2411:** double-blind, 8-week, parallel-group, active-controlled dose-escalation study evaluating the combination of aliskiren/HCTZ in comparison to HCTZ (with optional addition of amlodipine) in older patients (≥ 55 years)
Long-term open-label study	**Study SPP2360:** open-label, 24-week, non-comparative study in which patients were treated with an aliskiren-based regimen that included an optional add-on of HCTZ and amlodipine to control BP
Studies with the use of Aliskiren/amlodipine/HCTZ in patients whose BP was not controlled by aliskiren/amlodipine	
Long-term open-label study	**Study SPA2301:** open-label 54-week study evaluating the long-term safety and efficacy of aliskiren/amlodipine with optional addition of HCTZ [1] By study design, patients in these studies whose blood pressure was not controlled by aliskiren/hydrochlorothiazide or aliskiren/amlodipine received the add-on of amlodipine or hydrochlorothiazide. Therefore, a proportion of patients in these studies were treated with the combination of aliskiren/amlodipine/hydrochlorothiazide.
Additional Supportive Clinical Studies Submitted during Evaluation	
Long-term double-blind study	**Study SPA2307** 32 week, double-blind, parallelgroup, multicenter study to compare the efficacy and safety of initiating treatment with combination (aliskiren/amlodipine) therapy in comparison with the sequential add-on treatment strategies in patients with essentialhypertension .
Short-term active-controlled study	**SPA100AUS02:** 8 week, multicenter, randomized, double blind, active controlled, parallel group forced titration, study to evaluate the efficacy and safety of aliskiren/amlodipine/HCTZ compared to aliskiren/amlodipine in US minority patients with stage 2 hypertension.
Open label extension study	**Study SPHDE01:** Extension 1 to Study SPH100ADE01: An open-label, multicenter extension to evaluate the efficacy and safety of a 4 week therapy with amlodipine 5 mg and aliskiren 300 mg plus hydrochlorothiazide 25 mg in hypertensive patients not adequately responding to a 4 week therapy each with the combinations of candesartan 32 mg plus hydrochlorothiazide 25 mg followed by aliskiren 300 mg
Open label extension study	**Study SPADE01:** multicenter, sequential, open-label extension study where after a 2-week washout period, hypertensive patients (n=342) with a msDBP between 100-109 mmHg (inclusive) and msSBP between 160-179 mmHg (inclusive) were treated in Phase 1 (4 weeks) with olmesartan/amlodipine force titrated to 40/10 mg. Patients with an inadequate response (msDBP ≥ 90 mmHg; n=188) were treated in Phase 2 (4 weeks) with aliskiren/amlodipine 300/10 mg. Patients whose blood pressure was not controlled (msSBP ≥ 140 mmHg or msDBP ≥90 mmHg; n=65) after Phase 2 received triple therapy with aliskiren/amlodipine/HCTZ 300/10/12.5 mg for an additional 4 week extension.

1 By study design, patients in these studies whose BP was not controlled by aliskiren/HCTZ or aliskiren/amlodipine received the add-on of amlodipine or HCTZ. Therefore, a proportion of patients in these studies were treated with the combination of aliskiren/amlodipine/HCTZ.
BP=blood pressure; HCTZ=hydrochlorothiazide BP=blood pressure, HCTZ=hydrochlorothiazide

2.4.2. Pharmacokinetics

Rasitrio is a fixed combination of three drug substances already approved in EU, aliskiren, hydrochlorothiazide and amlodipine. According to the relevant CHMP Guideline on clinical development of fixed combination medicinal products the following studies are needed:

- Bioequivalence (BE) studies demonstrating BE between the free combination of the recognised reference formulations of the individual mono-components and the fixed combination final marketing formulation (FMI). In addition, because the pivotal clinical study was performed using the free combination amlodipine and hydrochlorothiazide clinical service formulations (CSFs) (in addition to aliskiren commercial tablets), BE between these CSFs and the FMI fixed dose combination has to be demonstrated. Three Bioequivalence studies were provided initially (CSAH100A2104, CSAH100A2105, CSAH100A2102) and two additional trials were conducted on request of the CHMP (SAH100A2110, SAH100A2111).
- Drug-drug interaction (DDI) study SAH100A2302.

In addition, due to the recognised food effect on aliskiren, a food-effect study was performed to evaluate the impact of a high fat meal on the pharmacokinetics of aliskiren, amlodipine, and hydrochlorothiazide following the administration of the 300/10/25 mg fixed combination FMI tablet (CSAH100A2101).

Summary of biopharmaceutic studies

Study No.	Objective	Population		Dosage form	Dose	N
CSAH100A2104	Relative Bioavailability FMI selection, safety and tolerability	HS	M/F	Aliskiren/amlodipine/HCTZ tablet (variant 01) Aliskiren/amlodipine/HCTZ tablet (variant 02) Aliskiren/amlodipine/HCTZ tablet (variant 03) Aliskiren/amlodipine/HCTZ tablet (variant 04) Aliskiren (RT) Amlodipine (CSF) HCTZ (CSF)	300/10/25 mg SD 300/10/25 mg SD 300/10/25 mg SD 300 mg SD 10 mg SD 25 mg SD	80
CSAH100A2105	Relative Bioavailability Safety and tolerability	HS	M/F	Aliskiren/amlodipine/HCTZ tablet (variant 05) Aliskiren/amlodipine/HCTZ tablet (variant 06) Aliskiren/amlodipine/HCTZ tablet (variant 07) Amlodipine (RT) Amlodipine (CSF) HCTZ (CSF)	300/10/25 mg SD 300/10/25 mg SD 300/10/25 mg SD 300 mg SD 10 mg SD 25 mg SD	72
CSAH100A2102	Definitive Bioequivalence Safety and tolerability	HS	M	Aliskiren/amlodipine/HCTZ tablet (FMI) Aliskiren (RT) Amlodipine (CSF) HCTZ (CSF)	300/5/25 mg SD 300 mg SD 5 mg SD 25 mg SD	109

Study No.	Objective	Population	Dosage form	Dose	N
CSPH100A2105	Definitive Bioequivalence	HS M/F	HCTZ (CSF)	25 mg SD	36
			HCTZ (RT – EU)	25 mg SD	
	Safety and tolerability		HCTZ (RT – Canada)	25 mg SD	
CSAH100A2101	High fat food Effect study	HS M/F	Aliskiren/amlodipine/HCTZ tablet (FMI)	300/10/25 mg SD	36
	Safety and tolerability				
CSPP100A2110	Effect of light meal on pharmacokinetics and pharmaco-dynamics of aliskiren	Mild to moderate hypertensive patients M/F	Aliskiren	300 mg QD for 28 days	122

HS = Healthy subjects; M = Male; F= Female; RT = Registered tablet; CSF= clinical service formulation; FMI = Final market image product;SD = Single dose

Bioequivalence: BE development programme was conducted with the fixed combination tablets and the 3 individual monotherapy products in free combination to allow bridging to the existing efficacy and safety data generated for the monotherapies and to support the substitution therapy indication. In response to the CHMP request, two additional bioequivalence studies under light meal conditions to demonstrate bioequivalence between the Rasitrio 300/5/25 mg and 300/10/25 mg final market image (FMI) and the EU approved formulations of respective monotherapies (study SAH100A2110 and study SAH100A2111) were also performed. Both studies are completed and the clinical, bio-analytical, and pharmacokinetic data bases have been locked. The study reports were provided and assessed before the finalisation of the CHMP opinion.

All BE studies were performed according to a single dose, cross-over design. A definitive BE study CSAH100A2102 demonstrated BE between the selected FMI formulation (300/5/25 mg dose strength) and the individual mono-therapy components. The individual mono-components used in this study were the same as those used in the pivotal clinical study. Aliskiren tablets were from the commercial formulation registered in EU, amlodipine capsules were commercially available Norvasc® tablets in capsules without backfill (Norvasc over-encapsulated 5 mg tablets), and hydrochlorothiazide was supplied as a clinical service formulation capsule. Therefore, the definitive BE study bridged the pivotal clinical study to the FMI fixed dose combination tablets.
For the sought substitution indication, BE should be demonstrated between the FMI tablet and the recognised reference formulations of the individual mono-components. This requirement was fulfilled for aliskiren. With regards to hydrochlorothiazide, BE was demonstrated between the FMI tablet and the CSF capsule. A separate study demonstrated BE between the hydrochlorothiazide CSF capsule and the EU-registered HCTZ tablets (Exidrex®). However, even though FMI tablet and EU-registered hydrochlorothiazide tablets are both bioequivalent to the hydrochlorothiazide CSF capsule, this does not imply that the FMI tablet is bioequivalent to the EU-registered hydrochlorothiazide tablet. With regards to amlodipine, BE was demonstrated between the FMI tablet and amlodipine capsules, which were over-encapsulated Norvasc® tablets in capsules without backfill. In order to support BE between Norvasc® tablets and over-encapsulated Norvasc tablets, *in vitro* dissolution data showing similarity in drug release were submitted. However, the data are insufficient to demonstrate BE between the FMI tablet and the EU reference amlodipine formulation (Norvasc® tablet). Additional investigations on the BE between the FDC 300/5/25 mg FMI tablet and the free combination of the mono-components showed adequate bridging between the main clinical studies and the FMI formulation, but not for demonstrating BE between the FMI tablet and the free combination of the EU recognised reference formulations of the individual mono-components. Furthermore, BE was demonstrated for amlodipine and hydrochlorothiazide. For aliskiren, however, BE was demonstrated in terms of AUC, but the lower boundary of the 90% CI for C_{max} ratio was slightly lower than 0.80 (90% CI: 0.76-0.90). it was claimed that the failure in demonstrating BE for C_{max} should not be clinically relevant. It is noted that, aliskiren is a highly variable drug (with regards to C_{max}), as defined by the new BE guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). If an intra-subject CV% of about 50% is applied, the 90% CI for C_{max} ratio would be within the widened acceptance interval, as calculated following the new BE guideline. However, the CHMP was of the opinion according to the current guidelines a widened acceptance interval should be prospectively defined, and a post hoc justification cannot be accepted. Therefore, the proof of BE between the FMI and the recognised reference formulations of the monocomponents was not sufficient and the CHMP considered this to be a major objection during evaluation process.

In BE studies, drug products were administered under fasting conditions, whereas the proposed SmPC recommends that Rasitrio should be taken with a light meal, in agreement with similar

recommendations for Rasilez (aliskiren) and Rasilez HCT. On one hand, it must be considered that BE studies conducted under fasted condition are more sensitive in detecting differences between drug products and therefore consist of the "worst case" to test bioequivalence. In addition, available data suggest that for aliskiren the food effect is mainly intrinsic to its physicochemical properties. On the other hand, comparison of all available food effect data show that AUC reduction range from -60% to -80%, which suggests that the food effect may also be partially dependent on the formulation. Therefore, this issue was raised as a major objection by the CHMP.

In response to the objections raised, two new BE studies (SAH100A2110 and SAH100A2111) were conducted.
Study CSAH100A2110 investigated the BE between the aliskiren/amlodipine/hydrochlorothiazide 300/10/25 FMI tablets and the free combination of the reference products: Rasilez® 300 mg, Norvasc® 10 mg, Esidrex® 25 mg. A total of 124 healthy male/female subjects between 18 and 55 years of age were enrolled and randomized to one of the two treatments, 111 subjects completed both treatments in three periods of the study.
Study CSAH100A2111 investigated the BE between the aliskiren/amlodipine/hydrochlorothiazide 300/5/25 FMI tablets and the free combination of the reference products: Rasilez® 300 mg, Norvasc® 5 mg, Esidrex® 25 mg. A total of 124 healthy male/female subjects between 18 and 55 years of age were enrolled and randomized, 110 subjects completed both treatment in three periods of the study. These studies were performed under light meal conditions. A widened acceptance interval for C_{max} ratio was prospectively defined in the study protocols, and the replicate study design allowed a determination of the within-subject CV% for C_{max}. Therefore, objections related to previous BE issues are considered resolved.

Food effect: A food-effect study evaluating the impact of a high fat meal on the pharmacokinetics of aliskiren, amlodipine, and hydrochlorothiazide following the administration of the 300/10/25 mg fixed combination FMI tablet was conducted. The intake of food did not influence absorption of amlodipine or hydrochlorothiazide but reduced aliskiren AUC and C_{max} by 79% and 89%, respectively, as compared to fasted conditions. This study further confirms the marked decrease in aliskiren bioavailability elicited by food. The mean decrease found in the present study (AUC: -79%) is similar to that found with the aliskiren/amlodipine fixed-dose combination (-80%) but higher than that found with aliskiren alone or aliskiren/hydrochlorothiazide (AUC reduction -60 to -70%). This suggests that the food effect may also be dependent on formulation.

Biowaiver: The biowaiver requested for 3 dose strengths (150/5/12.5 mg, 300/10/12.5 mg and 300/5/12.5 mg) was based on:
1) Pharmacokinetic linearity of the three active substances in the clinical dose range;
2) The same manufacturing process as that of the 300/10/25 mg or 300/5/25 mg FMI tablets used in the BE studies;
3) Compositional similarity or proportionality in active and inactive ingredients with the dose strengths used in the BE studies.
Dissolution data showing similarity in the *in vitro* dissolution profiles support the biowaiver request and the approach is acceptable because the criteria for biowaiver of the BE guideline are satisfied. Yet the dissolution data demonstrate similarity with the FMI formulations used in the BE studies, which were initially not demonstrated to be bioequivalent to the EU reference formulations of the mono-components, as discussed above. It should also be noted that calculation of similarity factor f2 was in several cases not in agreement with the BE guideline requirement that there should be no more than one mean value of > 85% dissolved for each formulation was often not fulfilled. With the use of several buffers, one or more active substances dissolved more than 85% already at the second time-point (20 min). Therefore, it is concluded that these dissolution data do not support the application and the CHMP requested the submission of appropriate dissolution testing by including more time points to ensure that at least three time points are used in the f2 similarity calculation. The newly provided dissolution data fulfilled the guideline requirements for a biowaiver request. Yet, the batches used in the repeated dissolution testing are the same as the ones used in the earlier testing. Following further request of the CHMP, additional dissolution testing was performed with the bio-batches used in the new bioequivalence trials SAH100A2110 and SAH100A2111. Dissolution similarity was demonstrated and granting of biowaiver is agreed.

Drug-drug interactions: Investigations on the interactions between aliskiren and amlodipine, or aliskiren and hydrochlorothiazide, were conducted as part of the development programme. It was found that amlodipine increased aliskiren AUC at steady-state by 29% and aliskiren did not change amlodipine pharmacokinetics. Furthermore, hydrochlorothiazide slightly reduced aliskiren C_{max} by 22%, with no effect on aliskiren AUC. Aliskiren slightly reduced both hydrochlorothiazide C_{max} (-26%) and AUC (-10%).

In addition, drug-drug interactions were evaluated in a sub-population of patients of the pivotal efficacy and safety study CSAH100A2302, using both, non-compartmental methods and a population pharmacokinetics approach. This was a parallel group study and samples were collected after 6 weeks of treatment from all treatment cohorts (aliskiren 300 mg/amlodipine 10 mg; aliskiren 300 mg/hydrochlorothiazide 25 mg; amlodipine 10 mg/hydrochlorothiazide 25 mg; aliskiren 300 mg/amlodipine 10 mg/hydrochlorothiazide 25 mg) from 0 (pre-dose) to 12 hours. A total of 77 patients participated in the pharmacokinetic substudy, with 17 patients in aliskiren/amlodipine/ hydrochlorothiazide combination, 19 patients in the amlodipine/hydrochlorothiazide, 18 patients in aliskiren/amlodipine, and 23 patients in aliskiren/ hydrochlorothiazide dual combination treatment arms. The comparative demographic and clinical data between all patients in the study and the pharmacokinetic substudy population show that the pharmacokinetic subpopulation is reasonably representative of the whole trial population.
For non-compartmental pharmacokinetic analysis, basic pharmacokinetic parameters were calculated; comparison of the mean C_{max} values and $AUC_{(tau)}$, at a steady state, for each of the individual drug were calculated. Lack of clinically significant drug-drug interaction due to the addition of the third drug was claimed based on the comparison of the geometric mean ratio and 90% CI for $AUC_{(tau)}$ and C_{max} values of individual drug from the triple and double combinations.
The population pharmacokinetic analysis used mixed effects modelling and was performed using NONMEM. A single pharmacokinetic model was built for each of the three compounds, with model parameters used to capture differences between the four treatment cohorts. During model development, a number of different diagnostic tools were applied at each modelling step. The final three models were qualified with residual diagnostics, predictive checks and bootstrapping. Drug-drug interactions were assessed *via* comparison of the population C_{max} values and AUC_{0-24} at six weeks for each of the individual drugs. Lack of significant drug-drug interaction due to the addition of the third drug was claimed based on the comparison of the population geometric mean ratio and its 90% CI for AUC_{0-24} and C_{max} values of individual drugs from the triple and double combinations. Both, the non-compartmental and the population pharmacokinetic analysis gave similar results, showing that in patients no clinically significant interaction occurred. Patients of the triple therapy group tended to have lower levels of all drugs, but it was convincingly demonstrated that this trend is not related to lower compliance and is not considered clinically relevant.
Nevertheless, as described earlier, healthy subjects showed that amlodipine may increase the exposure to aliskiren. Aliskiren related data showed that exposure is 50% higher in elderly subjects, as compared to young subjects and thus, the CHMP requested data on systemic exposure to the 3 components in the elderly. It was clarified that the pharmacokinetic subpopulation only included 1 patient aged >65 years treated with the triple therapy and 1 patient > 65 years treated with aliskiren/amlodipine. Therefore, valuable data of systemic exposure in the elderly could not be provided at this stage the claim of a substantial similarity in the safety profile of the triple and dual combinations is not supported by the CHMP. The lack of data of pharmacokinetic data for Rasitrio in the elderly and the increased risk of AEs potentially related to hypotension for the triple combination should is therefore reported in section 5.2. of the SmPC.

Absorption, Distribution and Elimination

Aliskiren: In fasting studies, following oral administration, aliskiren is rapidly absorbed with a T_{max} of 1-3 hours. The absolute bioavailability of aliskiren is approximately 2.6% and its oral bioavailability was greater following administration of capsules than oral solution (1.9 ± 0.7%). The absorption of aliskiren shows high variability. Typically, coefficients of variation for the plasma aliskiren AUC are in a range of 40-60% after an oral dose. The 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. The pharmacokinetics of aliskiren is linear over the therapeutic dose range of 150-300 mg. At a steady state, the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. Administration of aliskiren FMI tablets with a high fat meal resulted in a decrease in C_{max} and AUC of aliskiren by 85% and 71%, respectively. This issue is addressed in other chapters of this report. Aliskiren is moderately bound to human plasma protein (47-51%). The total plasma clearance (CL) is 9 L/h and the apparent volume of distribution at steady state (Vss) is 135 L indicating substantial distribution into the extra-vascular space. *In vitro* studies have demonstrated that aliskiren does not inhibit any of the CYP450 enzymes at therapeutic concentrations (IC50 > 200 µM). Following a p.o. administration of 300 mg [14C]-aliskiren, 91.5% of the radioactivity is recovered within 7 days. The majority of the radioactive dose (91%) is eliminated in the feces as unchanged drug (mostly unabsorbed) and 0.6% of the radio-labelled dose is eliminated in the urine.

Amlodipine is almost completely absorbed from the gastrointestinal tract. The absolute bioavailability is between 52% and 88%. Plasma concentrations of amlodipine rise gradually to peak 6-9 hr after oral administration. Changes in the dissolution rate do not influence the bioavailability of amlodipine. This was evidenced by the lack of a difference in the bioavailability of amlodipine when administered as suspension or immediate release tablet and as solution or immediate release capsule. Amlodipine exhibits linear pharmacokinetics in dose range of 5-10 mg. Oral absorption of amlodipine is not influenced by the presence of food. In healthy volunteers, amlodipine has a high volume of distribution of 21 L/Kg, which could be due to high membrane affinity of amlodipine. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. After a single intravenous or oral dose, the elimination half-life of amlodipine was approximately 40 hours.

Hydrochlorothiazide is rapidly absorbed after p.o. administration (T_{max} about 2 hours). Absolute bioavailability of hydrochlorothiazide is 60-80% after p.o. administration, with greater than 95% of the absorbed dose excreted in the urine. There is no change in the pharmacokinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once-daily to healthy subjects. Concomitant administration with food has been reported to both increase and decrease the systemic availability of the drug compared with the fasted state. The magnitude of these effects is small and not clinically important. Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. After an i.v. [^{14}C]-labeled dose of hydrochlorothiazide to two subjects, 90-93% of the dose was recovered in the urine and 1-4% in the feces. The majority of the dose was recovered in the first 12 hours after dosing. After a p.o. administration, about 95% of the absorbed dose is excreted as unchanged hydrochlorothiazide, and about 4% as the hydrolysate, 2-amino-4-chloro-*m*-benzenedisulfonamide. The distribution and elimination kinetics have generally been described by a bi-exponential decay function, with an apparent terminal elimination $T_{1/2}$ of 6-15 hours.

Dose proportionality and time dependencies

No specific pharmacokinetic studies were conducted.

Special populations

No specific pharmacokinetic studies were conducted.

Pharmacokinetic interaction studies

The potential for drug interaction aliskiren, amlodipine, and hydrochlorothiazide was evaluated in study CSAH100A2302 and this is described in sections above. No additional pharmacokinetic studies with the fixed combination formulation were conducted.

Pharmacokinetics using human biomaterials

No specific pharmacokinetic studies were conducted.

Pharmacodynamics

No specific pharmacodynamic studies investigating mechanism of action or primary and secondary pharmacological properties of the aliskiren/amlodipine/hydrochlorothiazide combination were performed. The pharmacodynamic properties of aliskiren, amlodipine and hydrochlorothiazide are well characterised and relevant information is reflected in their SmPCs. Furthermore, due to the differences in the mechanism of action of these drugs, pharmacodynamic interaction of aliskiren, amlodipine, and hydrochlorothiazide is unlikely.

2.4.3. Discussion on clinical pharmacology

The submitted clinical pharmacology studies focused on the evaluation of bioequivalence, drug-drug interactions and the food-effect.

Bioequivalence studies aimed to bridge FMI Rasitrio tablet with the free combination of amlodipine and hydrochlorothiazide clinical service formulations (CSFs) used in the pivotal clinical study along with the aliskiren commercial tablets. Furthermore, the studies aimed to demonstrate BE between the free combination of the recognised reference formulations of the individual mono-components and the fixed combination marketing formulation, which was only fulfilled for aliskiren. For hydrochlorothiazide, BE was demonstrated between the FMI tablet and the CSF capsule. A separate study demonstrated BE between the hydrochlorothiazide CSF capsule and the EU-registered tablets (Exidrex®). However, these data were insufficient for demonstration of BE between FMI tablet and the EU-registered hydrochlorothiazide. For amlodipine, BE was demonstrated between the FMI tablet and amlodipine capsules, which were over-encapsulated Norvasc® tablets in capsules without backfill. In order to support BE between Norvasc® tablets and over-encapsulated Norvasc tablets, *in vitro* dissolution data showing similarity in drug release were provided but were insufficient to demonstrate BE between the FMI tablet and the EU reference amlodipine formulation (Norvasc® tablet). In order to resolve these BE issues, two additional studies SAH100A2110 and SAH100A2111 were performed under light meal conditions in order to investigate BE with the EU reference hydrochlorothiazide and amlodipine formulations. Widened acceptance interval for C_{max} ratio was prospectively defined. The concerns regarding BE were therefore solved.

The BE studies were conducted under fasting conditions, whereas the proposed SmPC recommends Rasitrio to be taken with light meal. While it must be considered that BE studies conducted under fasted condition are more sensitive in detecting differences between products and, in addition, available data suggest that for aliskiren the food effect is mainly intrinsic to its physicochemical properties, comparison of all available food effect data show that AUC reduction range from -60% to -80%, which suggests that the food effect may also be partially dependent on drug formulation.

The request for biowaiver for 3 dose strengths (150/5/12.5 mg, 300/10/12.5 mg and 300/5/12.5 mg) was supported by dissolution data showing similarity in the *in vitro* dissolution profiles. Although the presented approach is acceptable, the dissolution data demonstrate similarity with the FMI formulations used in the BE studies, which were not demonstrated to be bioequivalent to the EU reference formulations of the mono-components. Therefore, dissolution testing was repeated; especially with the biobatches used in the two newly submitted bioequivalence studies and the biowaver concept was acceptable.

Drug-drug interactions were evaluated in a sub-population of patients of the pivotal efficacy and safety study CSAH100A2302 and based on its results, no clinically significant interactions occur between the three mono-components. The demographic and clinical data demonstrated that the sub-population of the study is representative of the whole population of study CSAH100A2302. It is, however, acknowledged that in healthy subjects amlodipine may increase the exposure to aliskiren, and the aliskiren data showed that exposure is 50% higher in elderly subjects, as compared to young subjects. drug interaction should also be evaluated in elderly subjects. The lack of data of pharmacokinetic data for Rasitrio in the elderly and the increased risk of adverse events potentially related to hypotension for the triple combination is therefore reported in the SmPC.

2.4.4. Conclusions on clinical pharmacology

Rasitrio is a fixed combination of aliskiren, amlodipine and hydrochlorothiazide, which are already approved in the EU. Their pharmacokinetic and pharmacodynamic profiles have been adequately characterised during the drug development of each substance. Several issues were identified specifically during Rasitrio development. These concerned the demonstration of bioequivalence between free combination of the recognised reference formulations of the individual mono-components and the fixed combination marketing formulation, conduct of clinical testing under fasting conditions and not with a light meal as recommended in the Rasitrio SmPC, and adequacy of submitted dissolution data in support of the biowaiver approached for three dose strengths, 150/5/12.5 mg, 300/10/12.5 mg, and 300/5/12.5 mg.
BE was correctly demonstrated between the FMI FDC formulation and the free combination of the EU reference products, under both fasting and fed (light meal) conditions. The biowaiver approach for three dose strengths is acceptable. The comparative dissolution data fulfil the guideline requirements for biowaiver. With respect to the examination of potential drug-drug interactions, the results of the pharmacokinetic sub-study of the clinical trial CSAH100A2302 indicated the lack of clinically significant interactions. Nevertheless, it is known that amlodipine may increase exposure to aliskiren, and the aliskiren data showed that exposure is 50% higher in elderly subjects, as compared to young subjects.

There are no adequate pharmacokinetic data available for the elderly and thus, the lack of this information is captured in Rasitrio SmPC.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Rasitrio clinical programme includes two pivotal studies (one short-term and one long-term) and no dose-response study. Doses of the 3 components in the combination are approved for marketing on the basis of experiences from earlier clinical studies and development programmes. The selection of doses for Rasitrio was based on current marketed and most commonly used doses of the individual components for the treatment of hypertension. The proposed range of Rasitrio doses is based on approved doses of the monotherapies, on the known dose dependent adverse reaction profile of amlodipine in the dose range 5-10 mg (e.g. oedema) and hydrochlorothiazide in the dose range 12.5-25 mg (e.g. hypokalaemia) and the relative absence of dose-dependent adverse reactions with aliskiren in the range 150-300 mg. Considering that the indication is requested for substitution therapy, the lack of complete data about efficacy and safety of lower doses of one or two components of the triple combination does not constitute an issue.

2.5.2. Main study(ies)

In support of the marketing authorisation application for Rasitrio, the following main clinical studies have been presented:

Main studies:
Study SAH 2302: Pivotal, 8 week double-blind active controlled study, to prove the superiority of the triple combination to double combination of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide in lowering blood pressure in patients with moderate or severe hypertension.
Study SAH 2301: Long-term efficacy safety study with 28 week treatment periods with the highest dose of the triple aliskiren/amlodipine/hydrochlorothiazide combination.

Supportive studies:
Study SPP 2344: double-blind active controlled 36 week study; the hydrochlorothiazide or amlodipine were administered "on demand".
Study SPP 2411: double-blind 8 week, active controlled dose escalation study. The use of amlodipine was "optional".
Study SPP 2360: open label 24 week non comparative study. The use of hydrochlorothiazide and amlodipine was "optional".
Study SPA 2301: open-label 54 week study. The use of hydrochlorothiazide was "optional".

During the course of evaluation of the marketing authorisation application for Rasitrio, results of further supportive clinical studies were provided; mainly in response to the objections and concerns raised by the CHMP. These are described in the appropriate sections of this report.

Study SAH 2302 is considered pivotal for the applied indication and will be described in details in the following sections. Data from other clinical trials are presented appropriately in the discussion on certain clinical aspects.

Summary of the pivotal efficacy study (Study SAH2302)

Study No.	Study objective, population	Patients random. / treated	Treatment duration	Treatment/dose (mg)	Primary efficacy endpoints
Study SAH2302	Efficacy/safety in patients with moderate to severe hypertension	1191/1188	8 wks	Ali/Aml (150/5 mg for 4 wks and 300/10 mg for 4 wks); Ali/HCTZ (150/12.5 mg for 4 wks and 300/25 mg for 4 wks); Aml/HCTZ (5/12.5 mg for 4 wks and 10/25 mg for 4 wks); Ali/Aml/HCTZ (150/5/12.5 mg for 4 wks with the first 3 days of Ali/HCTZ 150/12.5 mg and 300/10/25 mg for 4 wks)	Primary: Change from baseline in msSBP

Abbreviations: Ali=aliskiren; Aml=amlodipine; HCTZ=hydrochlorothiazide; msSBP=mean sitting systolic blood pressure; random.=randomized; and wk(s)=week(s).

Summary of key long-term efficacy and safety study (Study SAH2301)

Study No.	Study objective, population	Patients treated	Treatment duration	Treatment/dose (mg)	Key efficacy endpoints
Study SAH2301	Efficacy/safety in patients with essential hypertension	564	28 to 54 wks	Ali/HCTZ 300/12.5 mg 1 wk, Ali/Aml/HCTZ 300/5/12.5 mg 1 wk, force titrate up to Ali/Aml/HCTZ 300/10/25 mg for 26 wks (396 patients continued for a further 26 wks with Ali/Aml/HCTZ 300/10/25 mg)	Key efficacy: Change from baseline in msDBP, msSBP

Abbreviations: Ali=aliskiren; Aml=amlodipine; HCTZ=hydrochlorothiazide; msDBP=mean sitting diastolic blood pressure; msSBP=mean sitting systolic blood pressure; and wk(s)=week(s).

Summary of studies with the use of the aliskiren/amlodipine/HCTZ combination in patients whose BP was not controlled by double combination therapy (Studies SPP2344, SPP2411, SPP2360, and SPA2301)

Study No.	Study objective, population	Patients random./ treated (pts treated with Ali-triple comb.)	Treatment duration	Treatment/dose (mg)	Efficacy endpoints
Studies with the use of aliskiren/amlodipine/HCTZ in patients whose BP was not controlled by aliskiren/HCTZ					
Study SPP2344	Long-term efficacy and safety in elderly (≥65 years) patients with essential systolic hypertension	901/896 (51)[1]	36 wks (Ali/Aml/HCTZ escalation at wk 22)	Ali regimen: Ali 150 mg with optional up-titration to 300 mg with optional add-on HCTZ (12.5 or 25 mg) and additional optional add-on Aml (5 to 10 mg) Ram regimen: Ram 5 mg with optional up-titration to Ram 10 mg with optional add-on HCTZ (12.5 or 25 mg) and additional optional add-on Aml (5 to 10 mg)	**Primary:** Change from baseline in msSBP
Study SPP2411	Efficacy and safety in older patients (≥ 55 years) with stage 2 systolic hypertension	451/450 (29)[2]	8 wks (Ali/Aml/HCTZ escalation at wk 4)	Ali regimen: Ali/HCTZ 150/12.5 mg 2 wks, then 300/25 mg 7 wks with optional add-on of Aml 5 mg at wk 4 or 6; HCTZ regimen: HCTZ 12.5 mg 1 wk, then 25 mg 7 wks with optional add-on of Aml 5 mg at wk 4 or 6	**Primary:** Change from baseline in msSBP
Study SPP2360	Efficacy and safety in mild to moderate hypertension	--/256 (119)[3]	24 wks (Ali/Aml/HCTZ escalation at wk 16)	Ali 150 to 300 mg with add-on of HCTZ 12.5 to 25 mg and then add-on of Aml 5 mg to 10 mg	**Primary:** Proportion of patients who reached the BP target
Studies with the use of aliskiren/amlodipine/HCTZ in patients whose BP was not controlled by aliskiren/amlodipine					
Study SPA2301	Long-term safety/efficacy in mild to moderate hypertension	--/556 (86)[4]	54 wks (Ali/Aml/HCTZ escalation at wk 10)	Ali/Aml 150/5 mg for 2 wks, then Ali/Aml 300/10 mg for 52 wks (optional add-on of HCTZ 12.5 to 25 mg).	**Key efficacy:** Change in msDBP, msSBP

[1] A total of 51 patients received the aliskiren/amlodipine/HCTZ triple combination
[2] A total of 29 patients received the aliskiren/amlodipine/HCTZ triple combination
[3] A total of 119 patients received the aliskiren/amlodipine/HCTZ triple combination
[4] A total of 86 patients received the aliskiren/amlodipine/HCTZ triple combination
Abbreviations: Ali=aliskiren; Aml=amlodipine; BP=blood pressure; HCTZ=hydrochlorothiazide; msDBP=mean sitting diastolic blood pressure; msSBP=mean sitting systolic blood pressure; pts=patients; Ram=ramipril; random.=randomized; comb.=combination; and wk(s)=week(s).

Methods

Study Participants

Patients enrolled in the study SAH 2302 were 18 years or older, male or female, with either a diagnosis of moderate to severe hypertension (msSBP ≥ 160 mmHg and < 200 mmHg, and/or msDBP ≥ 100 mmHg and < 120 mmHg) at Visits 4, 5 or 6 (Qualifying BP visit), OR msSBP ≥ 180 mmHg and < 200 mmHg with msDBP ≥ 95 mmHg and < 120 mmHg, or msDBP ≥ 110 mmHg and < 120 mmHg with msSBP ≥ 150 mmHg and < 200 mmHg after at least one week of treatment with placebo (Visit 3 and on).

The main exclusion criteria were: Patients with an msSBP ≥ 200 mmHg or msDBP ≥ 120 mmHg at any time during the placebo run-in period were to be discontinued from the study, patients on four or more antihypertensive drugs at Visit 1, patients with previous or current diagnosis of hear failure, MI, heart block, atrial fibrillation, evidence of hepatic or severe renal impairment, history of TIA, cerebrovascular accident.

Treatments

The following drugs were provided in blisters that were identical in appearance:
Aliskiren 150 mg (aliskiren 150 mg) tablet, Aliskiren 300 mg (aliskiren 300 mg) tablet; Amlodipine 5 mg capsule, Amlodipine 10 mg capsule; Hydrochlorothiazide 12.5 mg capsule, Hydrochlorothiazide 25 mg capsule. Control drugs: placebos to Aliskiren 150 mg (aliskiren 150 mg) tablet, Aliskiren 300 mg (aliskiren 300 mg) tablet, Amlodipine 5 mg and 10 mg capsule, Hydrochlorothiazide 12.5 mg and 25 mg capsule. Patients were instructed to take two capsules and two tablets by mouth, with water each day in the morning at approximately 8am. A total of four pills were taken daily.

The study SAH 2302 comprised three periods.
Period 1 (Washout): maximum 4 wk, only for patients who were on antihypertensive medications, not requested for newly diagnosed patients who were enrolled directly into the 1 to 4 week single-blind placebo run-in period.
Period 2 (Single-blind placebo run-in): 1-4 week single-blind placebo run-in period to establish baseline BP and eligibility, weekly visits until BP requirements well fulfilled. If after a total of 4 weeks of single-blind placebo run-in treatment the patient did not meet the randomization criteria, the patient was to be discontinued from the trial and was not randomized.
Period 3 (Double-blind therapy): At Visit 6 (Day 1), patients were randomized in a double blind fashion to one of four treatment groups:
aliskiren 150 mg/amlodipine 5 mg,
aliskiren 150 mg/hydrochlorothiazide 12.5 mg,
amlodipine 5 mg/ hydrochlorothiazide 12.5 mg,
aliskiren 150 mg/ hydrochlorothiazide 12.5 mg for 3 days, then aliskiren 150 mg/amlodipine 5 mg/ hydrochlorothiazide 12.5 mg.
Patients remained on these doses for 4 weeks, and then were force titrated upward to the following doses for another 4 weeks:
aliskiren 300 mg/amlodipine 10 mg
aliskiren 300 mg/ hydrochlorothiazide 25 mg
amlodipine 10 mg/ hydrochlorothiazide 25 mg
aliskiren 300 mg/amlodipine 10 mg/hydrochlorothiazide 25 mg

A subgroup of patients participated in the ambulatory blood pressure monitoring (ABPM) substudy. Pharmacokinetic samples were collected on week 6 (Visit 11) of the study in a subgroup of patients.

Objectives

The primary objective of the study SAH 2302 was to demonstrate that a once daily dosing regimen of the triple combination of aliskiren/amlodipine/hydrochlorothiazide is superior to the double combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide and amlodipine/hydrochlorothiazide in lowering mean sitting systolic blood pressure (msSBP) in patients with moderate to severe hypertension.
Secondary objectives included evaluation of the blood pressure control rates (msSBP/msDBP < 140/90 mmHg) of the triple combination in comparison to the three double combinations in patients with moderate to severe hypertension; evaluate the DBP responder rates (msDBP < 90 mmHg and/or ≥ 10 mmHg reduction from baseline) of the triple combination in comparison to the three double combinations in patients with moderate to severe hypertension; evaluation of the SBP responder rates (msSBP < 140 mmHg and/or ≥ 20 mmHg reduction from baseline) of the triple combination in comparison to the three double combinations in patients with moderate to severe hypertension, and other parameters. The CHMP considered the objectives of the study as adequately defined.

Outcomes/endpoints

Primary efficacy variable: change from baseline (Visit 6) in msSBP.
Secondary efficacy variables: Change from baseline (Visit 6) in msDBP, percentage of patients achieving the BP control (msDBP < 90 mmHg and msSBP < 140 mmHg), percentage of patients

achieving the SBP response (msSBP < 140 mmHg or at least 20 mmHg reduction from baseline in msSBP), percentage of patients achieving the DBP response (msDBP < 90 mmHg or at least 10 mmHg reduction from baseline in msDBP), change from baseline in 24-hour ABPM (diastolic and systolic), change from baseline in daytime and nighttime ABPM (diastolic and systolic), biomarkers related to hypertension-related cardiac or renal risk were evaluated in this study, including, PRA and PRC.

Sample size

Approximately 2400 patients were planned to be screened worldwide to randomize approximately 1160 patients (290 randomized patients per treatment group). A sample size of 984 completed patients was targeted (246 per treatment arm). Assuming a drop-out rate of 15%, 1160 patients were planned to be randomized. The sample size was calculated for the primary variable, change from baseline in msSBP, assuming a standard deviation of 15 mmHg. The objective was to show that the triple combination was statistically superior to all three corresponding double combination treatments. To achieve this objective with an overall power of 90%, the sample size was calculated to simultaneously detect a treatment difference of at least 5 mmHg for all three corresponding pair-wise treatment comparisons, at a two-sided significance level of 0.05. Since it was necessary to show that the triple combination was statistically superior to all three double combination treatments, no multiple-comparisons adjustment of the type 1 error was needed.
For the critical secondary variables,
a sample size of 592 completed patients (148 per arm) was needed to detect a 5 mmHg difference in the change from baseline in MASBP (mean 24-hour systolic ABP) with 80% power. This calculation was based on a standard deviation of 13mmHg. Assuming a drop-out rate of 15%, a total of at least 700 patients (175 per arm) was necessary.

Randomisation

At Visit 6, all eligible patients were given a randomization number that assigned them to one of the treatment arms. The interactive voice response system (IVRS) was used to assign treatment following confirmation of the inclusion and exclusion criteria for the given patient.

Blinding (masking)

Patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomisation until database lock, using the following methods: (1) randomisation data were kept strictly confidential until the time of unblinding, and were only accessible to authorized personnel, (2) the identity of the treatments was concealed by the use of study drugs that appeared identical in packaging, labeling, and schedule of administration, (3) the appearance, weight, and odor of each study drug and its matching placebo was identical. Unblinding only occurred in case of patient emergencies and at the conclusion of the study SAH 2302.

Statistical methods

To assess the primary objective for the superiority of the triple combination of Rasitrio compared to the three double combinations in lowering msSBP, the primary variable at Week 8 endpoint (last post-baseline measurement prior to or on Week 8) was analysed using the ANCOVA model with treatment and region as two factors, and baseline as a covariate. The primary variable was also analysed at Week 8 for the Per-protocol population. Secondary efficacy analysis: the same analysis for msSBP was also performed for msDBP. The blood pressure control rates and responder rates were analysed using logistic regression models. For the low-dose combination treatments, all the analyses done at Week 8 endpoint were performed at Week 4 endpoint for the FAS population. Week 4 endpoint measurement was last post baseline measurement prior to or at Week 4. For patients who discontinued the study prematurely, the LOCF (last observation carried forward) approach was used to obtain their endpoint values for efficacy analyses.

Results

Participant flow, study SAH100A2302

The participants enrolled in study SAH100A2302 are described in the following table.

Patient disposition for each treatment group during the double-blind period (Enrolled set)

Disposition	Ali/Aml n (%)	Ali/HCTZ n (%)	Aml/HCTZ n (%)	Ali/Aml/HCTZ n (%)	Total n (%)
Enrolled					1909
Randomized	287	298[1]	296	310[1]	1191
Completed	266 (92.7)	276 (92.6)	279 (94.3)	285 (91.9)	1106 (92.9)
Discontinued	21 (7.3)	21 (7.0)	17 (5.7)	24 (7.7)	83 (7.0)
Reason for discontinuation (double blind)					
Adverse event(s)	7 (2.4)	2 (0.7)	8 (2.7)	11 (3.5)	28 (2.4)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Abnormal test procedure result(s)	1 (0.3)	3 (1.0)	1 (0.3)	2 (0.6)	7 (0.6)
Unsatisfactory therapeutic effect	2 (0.7)	3 (1.0)	1 (0.3)	2 (0.6)	8 (0.7)
Protocol deviation	2 (0.7)	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.3)
Patient withdrew consent	5 (1.7)	7 (2.3)	3 (1.0)	8 (2.6)	23 (1.9)
Lost to follow-up	4 (1.4)	6 (2.0)	2 (0.7)	1 (0.3)	13 (1.1)

[1] Two patients were randomized in an error and were assigned a randomization number (1 in the aliskiren/HCTZ group and 1 in the aliskiren/amlodipine/HCTZ group). Both patients were discontinued from the single-blind period without taking any double-blind study medication. Therefore, these patients were not counted as discontinued from the double-blind period.
Percentage (%) is calculated using the Randomized set as the denominator.

Recruitment

The first patient was enrolled on 20-Sep-2008 and the last patient completed study SAH 2302 on 07-Aug-2009. A total of 181 centres of 13 countries took part in the study (Australia, Canada, Denmark, Germany, Israel, Italy, Latvia, Lithuania, Romania, Sweden, Turkey, United States).

Conduct of the study

The protocol of study SAH2302 was not amended. There were no changes in study conduct. Prior to database lock, a change was made to the analysis plan to add efficacy analyses in patients with severe hypertension (msSBP ≥ 180 at baseline).

Baseline data

The baseline data are summarised in the table below.

Patient background characteristics by treatment group (Randomized set)

Demographic variable	Ali/Aml N = 287	Ali/HCTZ N = 298	Aml/HCTZ N = 296	Ali/Aml/HCTZ N = 310	Total N = 1191
Sex – n (%)					
Male	172 (59.9%)	175 (58.7%)	186 (62.8%)	187 (60.3%)	720 (60.5%)
Female	115 (40.1%)	123 (41.3%)	110 (37.2%)	123 (39.7%)	471 (39.5%)
Race – n (%)					
Caucasian	244 (85.0%)	251 (84.2%)	244 (82.4%)	263 (84.8%)	1002 (84.1%)
Black	26 (9.1%)	31 (10.4%)	35 (11.8%)	27 (8.7%)	119 (10.0%)
Asian	10 (3.5%)	10 (3.4%)	10 (3.4%)	12 (3.9%)	42 (3.5%)
Native American	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.3%)	2 (0.2%)
Pacific islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.1%)
Other	7 (2.4%)	5 (1.7%)	7 (2.4%)	6 (1.9%)	25 (2.1%)
Ethnicity – n (%)					
Hispanic/Latino	17 (5.9%)	18 (6.0%)	21 (7.1%)	20 (6.5%)	76 (6.4%)
Chinese	0 (0.0%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (0.3%)
Indian (Indian subcontinent)	7 (2.4%)	6 (2.0%)	4 (1.4%)	6 (1.9%)	23 (1.9%)
Mixed ethnicity	2 (0.7%)	2 (0.7%)	3 (1.0%)	1 (0.3%)	8 (0.7%)
Other	261 (90.9%)	271 (90.9%)	267 (90.2%)	282 (91.0%)	1081 (90.8%)
Age (years)					
n	287	298	296	310	1191
Mean	54.4	55.5	55.1	55.4	55.1
SD	11.33	10.75	10.86	10.54	10.86
Age group (years) – n (%)					
< 65	237 (82.6%)	242 (81.2%)	233 (78.7%)	251 (81.0%)	963 (80.9%)
≥ 65	50 (17.4%)	56 (18.8%)	63 (21.3%)	59 (19.0%)	228 (19.1%)
< 75	277 (96.5%)	285 (95.6%)	288 (97.3%)	299 (96.5%)	1149 (96.5%)
≥ 75	10 (3.5%)	13 (4.4%)	8 (2.7%)	11 (3.5%)	42 (3.5%)
Duration of hypertension history (years)					
n	279	289	281	301	1150
Mean	9.5	9.1	9.3	9.7	9.4
SD	7.89	8.52	8.15	8.43	8.25
n (naïve patients) – n (%)	8 (2.8%)	9 (3.0%)	15 (5.1%)	9 (2.9%)	41 (3.4%)
Body mass index (kg/m^2)					
n	286	297	296	309	1188
Mean	30.9	30.5	30.5	30.7	30.7
SD	5.88	6.20	5.75	5.73	5.84
BMI status – n (%)					
BMI < 20 kg/m^2	1 (0.3%)	2 (0.7%)	2 (0.7%)	0 (0.0%)	5 (0.4%)
20 kg/m^2 ≤ BMI < 25 kg/m2	35 (12.2%)	51 (17.1%)	40 (13.5%)	43 (13.9%)	169 (14.2%)
25 kg/m^2 ≤ BMI < 30 kg/m^2	97 (33.8%)	105 (35.2%)	117 (39.5%)	114 (36.8%)	433 (36.4%)
BMI ≥ 30 kg/m^2	153(53.3%)	139 (46.6%)	137 (46.3%)	152 (49.0%)	581 (48.8%)
Missing information	1 (0.3%)	1 (0.3%)	0 (0.0%)	1 (0.3%)	3 (0.3%)
Metabolic syndrome – n (%) #					
Yes	158 (55.1%)	152 (51.0%)	156 (52.7%)	150 (48.4%)	616 (51.7%)
No	129 (44.9%)	145 (48.7%)	140 (47.3%)	159 (51.3%)	573 (48.1%)
Diabetes – n (%) ##					
Yes	46 (16.0%)	40 (13.4%)	53 (17.9%)	33 (10.6%)	172 (14.4%)
No	241 (84.0%)	258 (86.6%)	243 (82.1%)	277 (89.4%)	1019 (85.6%)

SD = standard deviation.
Note: # metabolic syndrome = Yes, if any 3 of the following are true:
1. Waist circumference > 102 cm (40 in) for mean, 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).
From medical history and prior medication.

The CHMP noted that a total of 228 elderly patients (>65 years), 20% of randomised hypertensive subjects, were included in the study SAH 2302. Most of them (186 patients) were aged between 65 and 74 years (40-55 patients/arm). A total of 42 patients were randomised with age ≥75 (<14 patients/arm). Assuming a per-protocol set of 80%, there are complete data in 32-40 patients/arm in

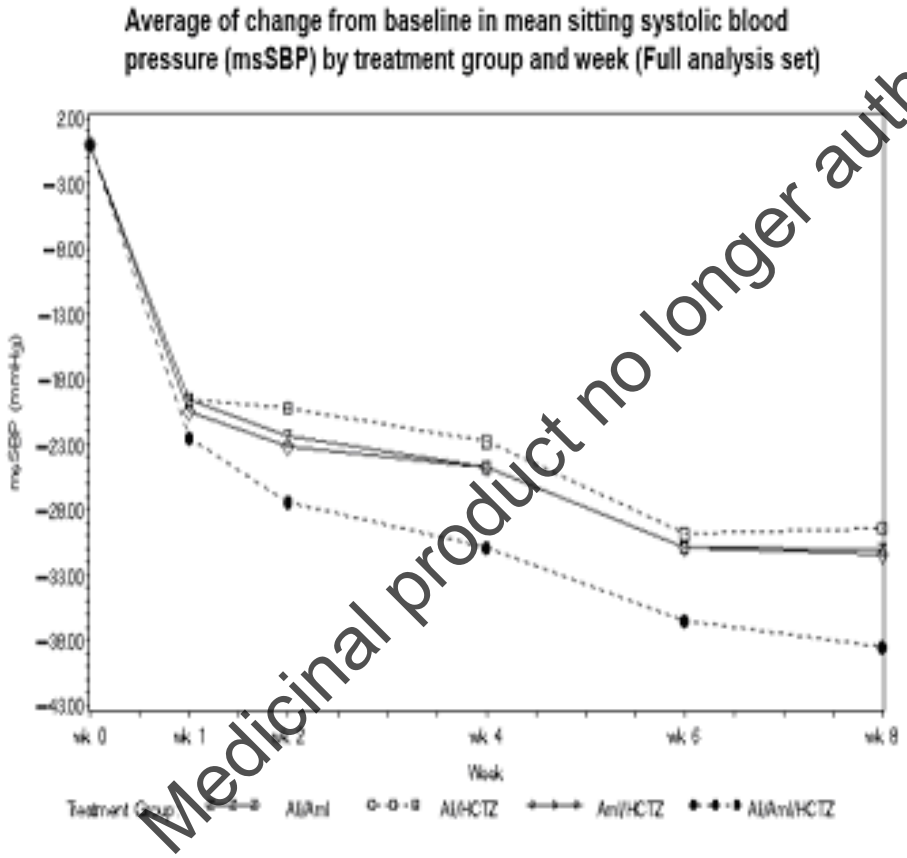
the age group 65-74 years and less than 11 patients/arm in the age group ≥75 years. The number of elderly subjects is too small to allow for any general claim in the elderly group.

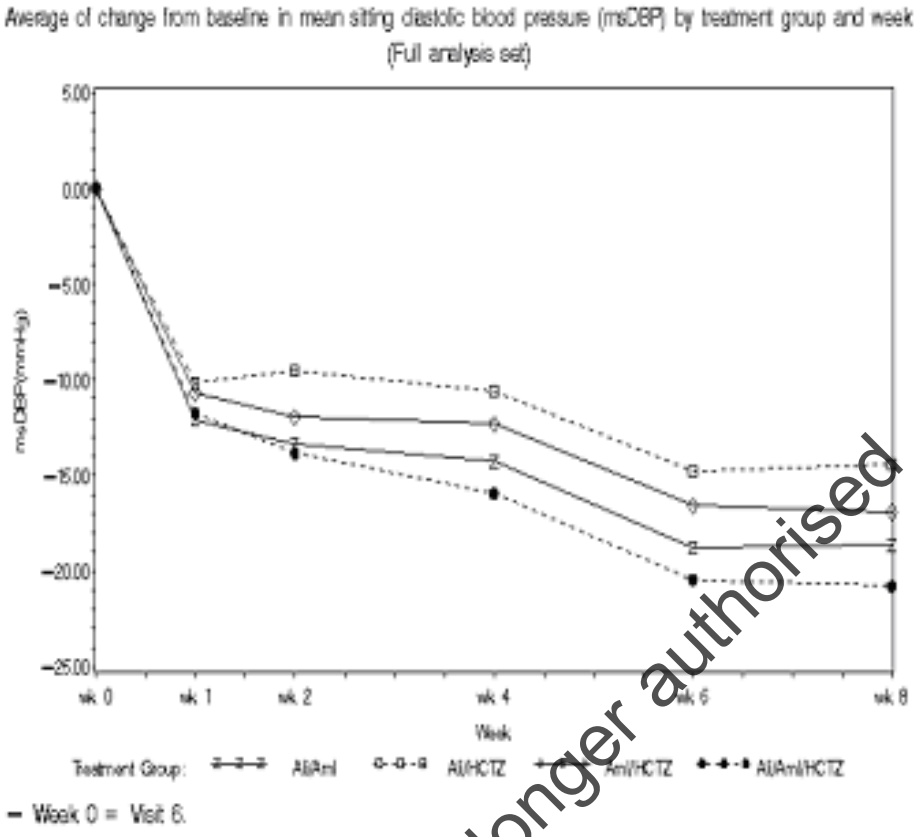
Numbers analysed

In study SAH100A2302 approximately 2400 male and female patients, with moderate to severe hypertension (msSBP of ≥160 mmHg and <200 mmHg, and/or msDBP ≥100 mmHg and <120 mmHg) were planned to be screened worldwide in order to randomize approximately 1160 patients (290 randomized patients per treatment group). Overall, 287 patients were randomized to aliskiren/amlodipine, 298 to aliskiren/hydrochlorothiazide, 296 to amlodipine/hydrochlorothiazide, and 310 to aliskiren/amlodipine/hydrochlorothiazide.

Outcomes and estimation

The changes in blood pressure observed during study SAH100A2302 are summarised in the graphs below. After the first 4-week treatment, there was an up-titration to the high dose.





After 4 weeks of treatment (low dose): The differences in observed for systolic and diastolic blood pressure reduction at week 4 are summarised in the following tables. The smallest difference was found in the comparison of aliskiren/amlodipine/hydrochlorothiazide to aliskiren/amlodipine (msSBP/DBP = 5.6/2.2, addition of hydrochlorothiazide to aliskiren/amlodipine), the largest difference was found in the comparison of aliskiren/amlodipine/hydrochlorothiazide to aliskiren/hydrochlorothiazide (msSBP/DBP = 8.7/5.1, addition of amlodipine to aliskiren/hydrochlorothiazide).

Statistical analysis change from baseline in mean sitting systolic blood pressure at Week 4 endpoint (Full analysis set)

Treatment group	N	LSM change from baseline (SE)	
Ali/Aml 150/5 mg	282	-25.14 (0.85)	
Ali/HCTZ 150/12.5 mg	296	-21.99 (0.83)	
Aml/HCTZ 5/12.5 mg	295	-24.47 (0.83)	
Ali/Aml/HCTZ 150/5/12.5 mg	308	-30.69 (0.81)	
Pairwise comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Ali/Aml/HCTZ vs Ali/Aml	-5.55 (1.15)	(-7.81, -3.28)	< 0.001*
Ali/Aml/HCTZ vs Ali/HCTZ	-8.70 (1.14)	(-10.94, -6.46)	< 0.001*
Ali/Aml/HCTZ vs Aml/HCTZ	-6.22 (1.14)	(-8.46, -3.98)	< 0.001*

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

Statistical analysis of change from baseline in mean sitting diastolic blood pressure at Week 4 endpoint (Full analysis set)

Treatment group	N	LSM change from baseline (SE)	
Ali/Aml 150/5 mg	282	-13.70 (0.53)	
Ali/HCTZ 150/12.5 mg	296	-10.74 (0.52)	
Aml/HCTZ 5/12.5 mg	295	-12.49 (0.52)	
Ali/Aml/HCTZ 150/5/12.5 mg	308	-15.87 (0.51)	
Pairwise comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Ali/Aml/HCTZ vs Ali/Aml	-2.17 (0.73)	(-3.60, -0.74)	0.003*
Ali/Aml/HCTZ vs Ali/HCTZ	-5.13 (0.72)	(-6.53, -3.72)	< 0.001*
Ali/Aml/HCTZ vs Aml/HCTZ	-3.38 (0.72)	(-4.79, - 1.97)	< 0.001*

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

After 8 week treatment (high dose): The differences in observed for systolic and diastolic blood pressure reduction at the study end are summarised in the following tables. The smallest difference was found in the comparison of aliskiren/amlodipine/hydrochlorothiazide to aliskiren/amlodipine (msSBP/DBP = 6.6/2.6, addition of hydrochlorothiazide 25 mg to aliskiren/amlodipine), the largest difference was found in the comparison of aliskiren/amlodipine/hydrochlorothiazide to aliskiren/hydrochlorothiazide (msSBP/DBP = 9.9/6.3, addition of amlodipine 10mg to aliskiren/hydrochlorothiazide).

Statistical analysis of change from baseline in mean sitting systolic blood pressure at Week 8 endpoint (Full analysis set)

Treatment group	N	LSM change from baseline (SE)	
Ali/Aml 300/10 mg	282	-31.37 (0.90)	
Ali/HCTZ 300/25 mg	296	-27.99 (0.88)	
Aml/HCTZ 10/25 mg	295	-30.77 (0.88)	
Ali/Aml/HCTZ 300/10/25 mg	308	-37.92 (0.86)	
Pairwise comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Ali/Aml/HCTZ vs Ali/Aml	-6.55 (1.22)	(-8.96, -4.15)	< 0.001*
Ali/Aml/HCTZ vs Ali/HCTZ	-9.93 (1.21)	(-12.31, -7.56)	< 0.001*
Ali/Aml/HCTZ vs Aml/HCTZ	-7.15 (1.21)	(-9.53, -4.78)	< 0.001*

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

Statistical analysis of change from baseline in mean sitting diastolic blood pressure at Week 8 endpoint (Full analysis set)

Treatment group	N	LSM change from baseline (SE)	
Ali/Aml 300/10 mg	282	-18.03 (0.57)	
Ali/HCTZ 300/25 mg	296	-14.32 (0.55)	
Aml/HCTZ 10/25 mg	295	-17.01 (0.55)	
Ali/Aml/HCTZ 300/10/25 mg	308	-20.63 (0.54)	
Pairwise comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Ali/Aml/HCTZ vs Ali/Aml	-2.60 (0.77)	(-4.11, -1.09)	< 0.001*
Ali/Aml/HCTZ vs Ali/HCTZ	-6.30 (0.76)	(-7.80, -4.81)	< 0.001*
Ali/Aml/HCTZ vs Aml/HCTZ	-3.59 (0.76)	(-5.08, -2.10)	< 0.001*

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

The observed blood pressure reduction was higher with the triple combination than with the double combinations after first 4-week treatment with the low-dose combinations (msSBP/msDBP = 31/16 *vs* 22-25/11-14) and after further 4-week treatment with the high-dose combinations (msSBP/msDBP = 38/21 *vs* 28-31/14-18). At both time points, the difference in the blood pressure reduction between triple combination and double combinations tended to be small when aliskiren/amlodipine/hydrochlorothiazide was compared to aliskiren/amlodipine. Analyses of 95%CIs indicate that, for msDBP, this difference was significant. When the percentage of patients with BP control (msSBP <140 mmHg and msDBP<90 mmHg) was analysed by a logistic-regression model, 62.3% of patients achieved BP control in the triple combination group at week 8 and this was statistically greater than each of the respective dual-combination groups as summarised in the table below.

Between treatment comparisons for blood pressure control at Week 8 endpoint (Full analysis set)

Pairwise comparison	Treatment A	Treatment B	
A vs B	n / N (%)	n / N (%)	p-value
Ali/Aml/HCTZ vs Ali/Aml	192 / 308 (62.3)	117 / 283[1] (41.3)	< 0.001*
Ali/Aml/HCTZ vs Ali/HCTZ	192 / 308 (62.3)	98 / 296 (33.1)	< 0.001*
Ali/Aml/HCTZ vs Aml/HCTZ	192 / 308 (62.3)	115 / 295 (39.0)	< 0.001*

Blood pressure control was defined as msDBP < 90 mmHg and msSBP < 140 mmHg.
P-values were from a logistic regression model with treatment and region as factors and baseline as covariate.
Baseline was the Visit 5 value.
N = Number of patients with baseline and Week 8 endpoint msDBP values.
* indicates statistical significance at 0.05 level.
[1] One patient in Ali/Aml did not have a baseline sitting blood pressure measurement; therefore this patient was included in this table

Analyses by age groups indicated that the reduction in msSBP and msDBP for age categories of <65, > 65 and > 75 were greater for the triple combination group compared to the respective dual-combination groups. In addition, a higher percentage of patients aged <65 years and > 65 years, at week 8 achieved BP control with the triple combination than with the respective dual-combination therapies, indicating that aliskiren/amlodipine/hydrochlorothiazide combination was effective irrespective of age.

Following the outcome of the GCP inspection requested by the CHMP, which identified a high number of aberrant BP readings that were not repeated, the CHMP asked for the conduct of statistical analyses excluding patients with aberrant readings in the overall study population as well as in patients aged >65 years and >75. Least squares mean changes from baseline in msSBP (primary variable) and msDBP, confidence intervals, and p-values from an ANCOVA model (containing treatment and region as factors and baseline as a covariate) are presented in the table below.

Between-treatment comparisons for change from baseline msBP at week 8 endpoint in patients without aberrant readings at both baseline and week 8 endpoint (SAH2302)

Treatment	N**	Change from Baseline				
		LS Mean Change[a]	SE	LS Mean difference[a,b] (Ali/Aml/HCTZ vs. other)	95% CI[a]	p-value[a]
msSBP (mmHg)						
Ali/Aml/HCTZ	160	-38.97	1.15			
Ali/Aml	147**	-31.25	1.20	-7.71 (1.63)	-10.90, -4.52	<0.001*
Ali/HCTZ	136**	-25.46	1.25	-13.50 (1.66)	-16.76, -10.2	<0.001*
Aml/HCTZ	148**	-29.21	1.20	-9.76 (1.62)	-12.95, -6.57	<0.001*
msDBP (mmHg)						
Ali/Aml/HCTZ	160	-21.07	0.73			
Ali/Aml	147**	-18.74	0.76	-2.33 (1.03)	-4.36, -0.31	0.024*
Ali/HCTZ	136**	-12.52	0.78	-8.54 (1.04)	-10.60, -6.49	<0.001*
Aml/HCTZ	148**	-16.40	0.75	-4.67 (1.02)	-6.68, -2.66	<0.001*

Baseline is week 0 value. Week 8 endpoint is value at week 8 or LOCF value

a: LSM, CI, and p-value from ANCOVA model containing treatment and region as factors and baseline as a covariate.

b: Difference in LS mean is for treatment - comparison

* indicates statistical significance at 0.05 level

** N is the number of patients without aberrant BP readings, and includes 1 patient each in ali/aml, ali/HCTZ, and aml/HCTZ treatment groups with missing post-baseline BP measurements. These 3 patients were excluded from the analysis and post text tables.

Despite the reduction in sample size due to the exclusion of patients with aberrant readings, the triple combination of aliskiren/amlodipine/hydrochlorothiazide achieved the primary objective of the study, demonstrating clinically meaningful and statistically significant greater reductions in msSBP compared with each dual combination therapy group at study endpoint. The superiority of the triple combination over each double combination was also demonstrated in msDBP. Importantly, the magnitude of the blood pressure reductions in these repeat analyses excluding patients without aberrant readings is comparable to the one seen in the overall population supporting that the exclusion of these patients does not affect the validity of the study conclusions.

Ancillary analyses

Ancilliary analyses have not been reported.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial SAH100A2302.

	Title: An 8 week, double-blind, randomized, parallel group, active controlled study to evaluate the efficacy and safety of the combination of aliskiren/amlodipine/HCTZ in patients with moderate to severe hypertension		
Study identifier	CSAH100A2302, EudraCT no. 2008-003199-23		
Design	This was an 8-week, double-blind, randomized, parallel group, active-controlled, multicenter study to evaluate the efficacy and safety of the combination of aliskiren/amlodipine/HCTZ in patients with moderate to severe hypertension (msSBP ≥ 160 and < 200 mmHg, and/or msDBP ≥ 100 mmHg and < 120 mmHg) at the qualifying BP visit). In addition, at the visit immediately prior to the qualifying visit, patients were also to have msSBP ≥ 145 mmHg and < 200 mmHg and msDBP ≥ 95 mmHg and < 120 mmHg). Alternatively, patients could be randomized if msSBP ≥ 180 mmHg and < 200 mmHg with msDBP ≥ 95 mmHg and < 120 mmHg, or msDBP ≥110 mmHg and < 120 mmHg with msSBP ≥ 150 mmHg and < 200 mmHg after at least one week of treatment with placebo. The study comprised a washout, a single-blind placebo run-in and a double-blind treatment phase. During the first four weeks of double-blind treatment, patients received low doses of either triple combination aliskiren/amlodipine/HCTZ or double combinations of aliskiren/amlodipine, aliskiren/HCTZ, and amlodipine/HCTZ. Patients were forced uptitrated to higher doses after 4 weeks for additional 4 weeks of double-blind treatment.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	8 weeks 1-4 weeks (if applicable) N/A	
Hypothesis	Superiority		
Treatments groups	aliskiren/amlodipine/HCTZ*		aliskiren 150 mg/ amlodipine 5 mg/HCTZ 12.5 mg (4 weeks), up titrated to aliskiren 300 mg/amlodipine 10 mg/HCTZ 25 mg. 8 weeks total treatment period, 310 patients randomized
	aliskiren/HCTZ		aliskiren 150 mg/HCTZ 12.5 mg (4 weeks) up titrated to aliskiren 300 mg/HCTZ 25 mg. 8 weeks total treatment period, 298 patients randomized
	aliskiren/amlodipine		aliskiren 150 mg/amlodipine 5 mg (4 weeks) up titrated to aliskiren 300 mg/amlodipine 10 mg. 8 weeks total treatment period, 287 patients randomized
	amlodipine/HCTZ		amlodipine 5 mg/HCTZ 12.5 mg (4 weeks) up titrated to amlodipine 10 mg/HCTZ 25 mg. 8 weeks total treatment period, 296 patients randomized
	*		Patients randomized to aliskiren/amlodipine/ HCTZ began treatment with aliskiren 150 mg/ HCTZ 12.5 mg for 3 days, after which amlodipine 5 mg was added. The dose of aliskiren 150 mg/amlodipine 5 mg/HCTZ 12.5 mg was continued for the remainder of the first 4 weeks of double-blind treatment.
Endpoints and definitions	Primary endpoint	Change from baseline msSBP	Demonstrate that a once daily dosing regimen of the triple combination of aliskiren/ amlodipine/HCTZ 300/25/10 mg is superior to the double combinations of aliskiren/ amlodipine 300/10 mg, aliskiren/HCTZ 300/25 mg and amlodipine/HCTZ 10/25 mg in lowering mean sitting systolic blood pressure (msSBP) in patients with moderate to severe hypertension.
	Secondary endpoint	Change from baseline msDBP	Demonstrate that a once daily dosing regimen of the triple combination of aliskiren/ amlodipine/HCTZ 300/25/10 mg is superior to the double combinations of aliskiren/ amlodipine 300/10 mg, aliskiren/HCTZ 300/25 mg and amlodipine/HCTZ 10/25 mg in lowering mean sitting diastolic blood pressure (msDBP) in patients with moderate to severe hypertension.
Database lock	17 September 2009		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat 8 weeks				
Descriptive statistics and estimate variability	Treatment group	aliskiren/amlodipine/HCTZ	aliskiren/ HCTZ	aliskiren/ amlodipine	amlodipine/ HCTZ
	Number of subject	308	296	282	295
	Change in msSBP (mmHg) from baseline at Wk 8 (LOCF) Mean	-37.4	-28.2	-30.6	-30.8
	Standard Deviation (SD)	17.87	16.78	15.45	16.20
	Change in msDBP (mmHg) from baseline at Wk 8 (LOCF) Mean	-20.3	-13.9	-18.4	-16.6
	Standard Deviation (SD)	10.06	10.78	9.77	9.74

Effect estimate per comparison	Primary endpoint (Change from baseline in msSBP)	Comparison groups	aliskiren/amlodipine/HCTZ vs. aliskiren/amlodipine
		Least Squares mean (LSM) Difference	-6.55
		Standard Error (SE)	1.22
		P-value	<0.001*
	Primary endpoint (Change from baseline in msSBP)	Comparison groups	aliskiren/amlodipine/HCTZ vs. aliskiren/HCTZ
		Least Squares mean (LSM) Difference	-9.93
		Standard Error (SE)	1.21
		P-value	<0.001*
	Primary endpoint (Change from baseline in msSBP)	Comparison groups	aliskiren/amlodipine/HCTZ vs. amlodipine/HCTZ
		Least Squares mean (LSM) Difference	-7.15
		Standard Error (SE)	1.21
		P-value	<0.001*
	Secondary endpoint (Change from baseline in msDBP)	Comparison groups	aliskiren/amlodipine/HCTZ vs. aliskiren/amlodipine
		Least Squares mean (LSM) Difference	-2.60
		Standard Error (SE)	0.77
		P-value	<0.001*
	Secondary endpoint (Change from baseline in msDBP)	Comparison groups	aliskiren/amlodipine/HCTZ vs. aliskiren/HCTZ

		Least Squares mean (LSM) Difference	-6.30
		Standard Error (SE)	0.76
		P-value	<0.001*
	Secondary endpoint (Change from baseline in msDBP)	Comparison groups	aliskiren/amlodipine/HCTZ vs. amlodipine/HCTZ
		Least Squares mean (LSM) Difference	-3.59
		Standard Error (SE)	0.76
		P-value	<0.001*
Notes	* indicates statistical significance at 0.05 level		
Analysis description	**Primary Analysis** To assess the primary objective for the superiority of the triple combination of aliskiren/HCTZ/amlodipine 300/25/10 mg compared to the three double combinations (aliskiren/HCTZ 300/25 mg, aliskiren/amlodipine 300/10 mg, and HCTZ/amlodipine 25/10 mg) in lowering msSBP, the primary variable at Week 8 endpoint (last post-baseline measurement prior to or on Week 8) was analyzed using the ANCOVA model with treatment and region as two factors, and baseline as a covariate. This is the primary model. Three pair-wise treatment comparisons (triple combination versus the three dual therapies) were made based on the primary model. The triple combination was considered more effective than the dual therapies if all pair-wise comparisons were statistically significant in favor of the combination. The statistical test for each of the pair-wise comparisons was made at the two-sided significance level of 0.05. Ninety-five percent confidence intervals were provided.		

Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analysis of clinical data was performed to evaluate the efficacy of aliskiren on blood pressure by gender based on placebo-controlled studies of aliskiren (8 weeks duration). The below table presents the aliskiren results for msDBP and msSBP change from baseline with and without placebo-subtracted values for males and females.

Change from baseline to endpoint in msDBP and msSBP by gender with aliskiren – pooled placebo controlled studies (ITT population)

Treatment	N		Baseline Mean		Endpoint Mean		Change from Baseline: Mean		Change from Baseline: Placebo-subtracted	
Gender	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
msDBP										
Placebo	461	315	99.5	98.6	94.3	91.0	-5.3	-7.6		
Ali 75 mg	278	197	99.6	99.0	91.0	89.7	-8.6	-9.3	-3.3	-1.7
Ali 150 mg	468	298	99.5	98.8	90.8	88.2	-8.7	-10.6	-3.4	-3.0
Ali 300 mg	438	326	99.7	98.8	89.1	86.6	-10.6	-12.2	-5.3	-4.6
Ali 600 mg	165	130	99.5	99.1	88.3	85.8	-11.2	-13.2	-5.9	-5.6
msSBP										
Placebo	461	315	151.9	153.7	147.3	146.4	-4.6	-7.3		
Ali 75 mg	278	197	152.4	153.8	143.4	143.0	-9.0	-10.7	-4.4	-3.4
Ali 150 mg	468	298	153.2	153.5	142.8	140.3	-10.4	-13.2	-5.8	-5.9
Ali 300 mg	438	326	153.2	153.9	139.6	137.1	-13.6	-16.7	-9.0	-9.4
Ali 600 mg	165	130	151.7	152.8	138.0	135.3	-13.7	-17.6	-9.1	-10.3

Studies: Study SPP2201, Study SPP2203, Study SPP2204, Study SPP2308, Study SPP1201

Females had a slightly greater placebo response than males for reductions in SBP and DBP for both, the responder rate and the control rate. When the placebo-subtracted responses were compared, they were similar for both genders. There is no evidence of a gender difference in response to aliskiren.

In an effort to more precisely prospectively identify patients that would most benefit from the triple combination, additional analyses were performed. One dataset consisted of studies that permitted the optional addition of hydrochlorothiazide to patients not achieving blood pressure control with the double combination aliskiren/amlodipine. The second dataset consisted of studies that permitted the

optional addition of amlodipine to patients not achieving blood pressure control with the double combination aliskiren/hydrochlorothiazide. The population characteristics of the patients that were adequately treated with a double combination or that required the triple combination were generally similar and representative of the enrolled hypertension population. Patients with higher baseline blood pressures and diabetic patients were more likely to require triple therapy. Other baseline characteristics male gender, black ethnicity, overweight and overweight-associated disorders (metabolic syndrome and diabetes) were weak predictors of the need of the triple combination for adequate hypertension control.

Clinical studies in special populations

No studies in special populations relevant to the triple combination have been included.

Supportive studies

Study SAH100A2301: This is a long-term uncontrolled clinical study pertinent to the claimed indication. A 28 to 54-week, open-label, multicenter study to assess the long-term safety and tolerability of the combination of aliskiren/amlodipine/hydrochlorothiazide in patients with essential hypertension. Efficacy was the secondary objective of the study and the key efficacy variables included msSBP/msDBP reduction from baseline, BP control and response rate: % of patients achieving the target of < 140/90 mmHg, and achieving a response in msDBP (msDBP < 90 mmHg or a ≥ 10 mmHg decrease from baseline) and msSBP (msSBP < 140 mmHg or a ≥ 20 mmHg decrease from baseline). The study was comprised of two periods: washout and treatment period. A total of 635 patients entered the washout phase, but 71 patients (11.2%) discontinued due to abnormal test or not fulfilling the BP criteria. A total of 493 patients (87.4%) completed the study; the main reason for discontinuation was an adverse event. It was noted that only 206 patients completed both periods of the study (2x6 months) and they received only the high dose combination (aliskiren/amlodipine/hydrochlorothiazide 300/10/25 mg), which is acceptable only for screening of the most serious AEs. In general, based on the results of this study, the safety profile of the combination appears to be consistent with that observed in previous short term studies. The majority of reported AEs were mild or moderate in severity.

Study SPP100A2411: An 8-week randomised, double-blind, parallel-group, multicenter, active-controlled dose escalation study to evaluate the efficacy and safety of aliskiren HCTZ (300/25 mg) compared to HCTZ (25 mg) in older patients with stage 2 systolic hypertension.
Results of this study are not relevant for the claimed indication for the triple combination because only 29 patients received aliskiren/amlodipine/HCTZ triple combination treatment. Such a small number do not allow any conclusion on the BP lowering effect of the triple combination. Results of the study duplicate the previous evidence that HCTZ and aliskiren, when combined in a FDC independently contribute in lowering BP levels. This evidence was adequately showed in the studies included in the dossier of Rasilez HCT FDC as stated by the Applicant in the Introduction of the two pivotal studies.

Study SPP100A2344: A 36-week randomised, double-blind, parallel group, multicenter, active-controlled, optional titration study comparing an aliskiren-based regimen (150 mg–300 mg) to a ramipril-based regimen (5 – 10 mg) in patients $\geq$ 65 years old with systolic essential hypertension. Initially, aliskiren or ramipril was administered at day 1. In patients with uncontrolled blood pressure, the study protocol included the administration of hydrochlorothiazide as a second optional drug at visit 7 and of amlodipine also as a third optional drug at visit 9. This study is of limited relevance for the triple combination. The subgroup treated for at least 24 weeks with the triple combination accounted for 7% of the enrolled cohort; the number of patients treated for at least 24 weeks with the triple combination (n=31) is far below the minimum threshold requested by CHMP guidelines for long-term studies on safety.

Study SPA2301: This was a 54-week, open-label, multicenter study to assess the long-term safety and tolerability of the combination of aliskiren 300mg/amlodipine 10mg in patients with essential hypertension. Results of this study are not essential for the claimed indication; its design includes administration of hydrochlorothiazide as a third optional drug only in patients with uncontrolled blood pressure and only after 72 days of treatment with aliskiren/amlodipine. The results are certainly affected by a substantial selection bias because the subgroup treated with hydrochlorothiazide accounted for 15.5% of the enrolled cohort. Moreover, the total number of patients completing the study was 81 at 6-month end-point and 74 at 12-month end-point and these numbers are far below the minimum required threshold.

Study SPP2360: This was a 24-week, open-label, non-comparative, multicenter study to assess the efficacy and tolerability of an aliskiren-based treatment (150mg – 300mg) in patients with mild to moderate hypertension. First step of treatment was the administration of aliskiren at day 1. In patients with uncontrolled blood pressure, the study protocol included the administration of hydrochlorothiazide as a second optional drug at visit 5 and of amlodipine also as a third optional drug at visit 7. The study is of limited relevance as the subgroup treated with the triple combination, for at least 8 weeks, accounted for only 24% of the enrolled population (62/256), and 0% of the enrolled population was treated with the triple combination for 10 or more weeks (0/256). For the subgroup of 62 patients with complete 8-week data, the design of the study (open label and without control), the selection bias (24% of the original cohort), and the limited sample size (n=62) make the results unreliable for evaluation of both efficacy and safety.

Study SPA2307 was a randomised, double blind, parallel group study. After washout and placebo run-in, eligible patients were randomised in a 1:1:2 ratio to one of three treatment groups: aliskiren 150 mg (N=318), amlodipine 5 mg (N=316) or the combination of aliskiren/amlodipine 150/5 mg (N=620) for 8 weeks. There was forced titration in each group so that by the start of week 16 patients in all three groups were receiving aliskiren/amlodipine 300/10 mg. At the start of week 24, patients with uncontrolled BP (msSBP > 140mmHg or msDBP > 90mmHg) received hydrochlorothiazide 12.5mg in addition to their regimen for additional 8 weeks. The number and percentage of patients who did not achieve BP control with aliskiren/amlodipine was 221 (36.6%) in the total study population. In the subgroup of patients who had not reached BP control while on dual therapy with aliskiren/amlodipine, msSBP/msDBP was 148/85 mmHg in the total population at week 24. The triple combination of aliskiren/amlodipine/hydrochlorothiazide produced additional reductions in msSBP and in msDBP across the three randomized groups, as summarised in the table below.

Additional reductions in msSBP and msDBP from week 24 to week 32 by randomized treatment regimen in patients who received Ali/Aml/HCTZ (Study SPA2307)

	Ali/Aml regimen		**Ali regimen**		**Aml regimen**	
	Week 24	Change	Week 24	Change	Week 24	Change
N	164	164	79	79	83	83
msSBP (mmHg)	146.9	-5.0	148.1	-6.9	148.0	-3.7
msDBP (mmHg)	84.1	-1.8	84.9	-2.8	87.9	-2.1

The additional reduction in msSBP/msDBP was significant only in one of the three original arms, i.e., the arm which was originally treated with aliskirenamlodipine. Moreover, compared to the dual combination aliskiren/amlodipine, the triple combination of aliskiren/amlodipine/hydrochlorothiazide produces a significant reduction of blood pressure only in a limited percentage of patients with uncontrolled hypertension. Moreover, the lack of a parallel arm maintained on the dual combination aliskiren/amlodipine raises the possibility that results were affected by seasonal effects or other confounders.

Study SPAUS02: was an 8-week, prospective, multicenter, randomised, double-blind, active controlled, parallel-group, forced titration study comparing the efficacy and safety of a triple combination aliskiren/amlodipine/hydrochlorothiazide treatment regimen to a double combination aliskiren/amlodipine regimen in patients of self-identified minority background, with Stage 2 hypertension (baseline msSBP ≥160 mmHg and <200 mmHg). A total of 203 patients were randomised to the triple combination regimen and 209 patients to the aliskiren/amlodipine regimen. Study medication was administered without regard to meals. Mean age was approximately 55 years in both arms. The percentage of patients with age ≥75 years was low, ≤3% in the two arms. The percentage of patients achieving BP control was greater in the aliskiren/amlodipine/hydrochlorothiazide at week 2, week 4 and week 8. Nevertheless, the 1-week duration of each step in this forced titration study (1 week – 1 week – 2 weeks – 4 weeks) cannot rule out the possibility that the progressive reduction in blood pressure in steps after week 1 reflected not only the effect of the change in the treatment but also the effects of the prolongation of the treatment of the preceding step. The limited duration of the study does not allow for firm conclusions on safety.

Study SPHDE01 and Study SPADE01: were non-responder design trials in patients not adequately controlled on dual therapies and were conducted in Germany. Study medication was administered without regard to meals in Study SPHDE01 and with a light meal in Study SPADE01.

Supportive Study SPHDE01 was a multicenter, sequential, open-label trial where after a 2-week washout period, hypertensive patients (n=186) with a msDBP between 100-109 mmHg were treated in Phase 1 (4 weeks) with candesartan/hydrochlorothiazide 16/12.5 mg for 1 week and force titrated to 32/25 mg. Patients with an inadequate response (n=123) were treated in Phase 2 (4 weeks) with aliskiren/hydrochlorothiazide 300/25 mg. Patients with an inadequate response (n=61) after Phase 2 received triple therapy with aliskiren/amlodipine/ hydrochlorothiazide 300/5/25 mg for additional 4 weeks. Study medication was administered without regard to meals. Clinically relevant further reductions in both systolic and diastolic blood pressure were observed with the triple combination. Administration of the triple combination allowed 36.1% of the patients not controlled at the end of Phase 2 to achieve control of their blood pressure levels. The lack of a parallel arm maintained on the dual combination aliskiren/hydrochlorothiazide raises the possibility that results could have been affected by seasonal effects or other confounders.
Supportive Study SPADE01 was similar in design to Study SPHDE01; a multicenter, sequential, open-label trial where after a 2-week washout period, hypertensive patients (n=342) with a msDBP between 100-109 mmHg and msSBP between 160-179 mmHg were treated in Phase 1 (4 weeks) with olmesartan/amlodipine force titrated to 40/10 mg. Patients with an inadequate response were treated in Phase 2 (4 weeks) with aliskiren/amlodipine 300/10 mg. Patients whose blood pressure was not controlled (n=65) after Phase 2 received triple therapy with aliskiren/amlodipine/hydrochlorothiazide 300/10/12.5 mg for additional 4 weeks. Study medication was administered with a light meal. Mean age of patients was approximately 60 years. The CHMP noted that the percentage of patients with age ≥75 years was not given. Clinically relevant additional reductions in both msSBP and msDBP were observed in patients who received triple therapy as shown in the table below.

Effect of aliskiren/amlodipine/HCTZ on blood pressure in patients not adequately controlled with aliskiren/amlodipine (Study SPADE01)

	End Phase 2 (±SD) n=65	End Extension (±SD) n=65	Change* (95% CI)	p-value
msSBP (mmHg)	147.5 ± 8.24	139.4 ± 9.82	8.1 (5.68-10.46)	< 0.0001
msDBP (mmHg)	93.1 ± 4.62	86.4 ± 7.75	6.7 (5.11-8.20)	< 0.0001
* Reduction from end phase 2				

The additional blood pressure reduction induced by the triple combination allowed 46.2% of the patients not controlled at the end of Phase 2 to achieve control of their blood pressure levels. The lack of a parallel arm maintained on the dual combination aliskiren/amlodipine raises the possibility that results were affected by seasonal effects or other confounders. Furthermore, the 1-week duration of the step after the wash-out period in this forced titration study (week – 1) cannot rule out the possibility that the maximal antihypertensive effect was not yet reached by the combination olmesartan/amlodipine when uptitration to the triple combination was performed.

In general, the CHMP considered that the newly submitted results from these four additional clinical trials are of limited significance and provide only limited information about the efficacy and safety of the triple combination as compared to the double combination.

2.5.3. Discussion on clinical efficacy

The present application for marketing authorisation of Rasitrio is based on the wide therapeutic experience of aliskiren, amlodipine and hydrochlorothiazide. The CHMP Guideline on clinical investigation of medicinal products in the treatment of hypertension (CPMP/EWP/238/95 Rev. 3) states that a fixed combination can be approved solely on the basis of bioequivalence studies if all components of the combination have a wide therapeutic experience. If this condition is not met, additional clinical trials including factorial and long term safety studies are requested to support the safety and efficacy of the proposed combination. Following the CHMP's request to submit sufficient epidemiological or other data to support the claim that there is a wide therapeutic experience of aliskiren, amlodipine and hydrochlorothiazide use in combination, further data were provided to demonstrate that:

- Aliskiren has been evaluated in more than 37,000 patients in clinical trials during its development and after its registration, either as aliskiren monotherapy or in combination with other anti-hypertensive agents. Aliskiren tablets (150 mg and 300 mg) are now approved in over 101 countries worldwide and are being used in adults for the treatment of hypertension. Based on a review of the prescription databases in 6 countries (Germany, Italy, Netherlands, Spain, Canada, and US), it can be

estimated that a total of 756 041 patients received aliskiren monotherapy from launch to January 2010 and that among these, 82 690 (11%) patients are estimated to have also received amlodipine and hydrochlorothiazide.
- Clinical data from two pivotal studies (SAH2302 and SPA2301) and from 8 supportive trials were provided to support the benefit/risk profile of the combination.
- In support of the substitution indication, an exhaustive bioequivalence program was conducted.

The rational for the selection of the five doses for Rasitrio (aliskiren/amlodipin/hydrochlorothiazide 150/5/12.5 mg; 300/5/12.5 mg; 300/10/12.5mg; 300/5/25 mg and 300/10/25 mg) has also been discussed; the main reason for this selection was the inclusion of combinations of 300 mg aliskiren with low doses of amlodipine and hydrochlorothiazide in order to limit the well known dose-dependent adverse reactions, mainly oedema and hypokalaemia, associated with the use of amlodipine and hydrochlorothiazide. In principle, this does not solve the issue of the lack of complete data about efficacy and safety of the combination with lower doses of one or two components of the triple FDC. However, once the combination product is in therapeutic use, it will be possible to prescribe it only to patients who are adequately controlled with the concomitant administration of the already used doses of the three monocomponents.

Most of the efficacy data of the triple combination originate from the pivotal short term study SAH100A2302, which aimed to evaluate efficacy of aliskiren/amlodipine/hydrochlorothiazide in patients with uncomplicated stage 2-3 hypertension (moderate to severe).

No relevant information on the efficacy of the triple combination may be inferred from the supportive studies submitted with the present application due to the following reasons:

- The scattered number of patients receiving triple FDCs makes supportive studies of limited value for the proposed FDCs.
- Supportive studies suffer from the design bias of having selected those patients for the triple FDC combination, who were not adequately controlled by either monotherapy or association therapy with two monocomponents. This design increases the likelihood that the triple combination shows increased efficacy.
- In several supportive trials, the lack of a parallel arm maintained on the dual combination aliskiren/amlodipine raises the possibility that results were affected by seasonal effects or other confounders.
- The studies do not add significant information about the efficacy of the triple combination in patients with age ≥75 years, a point which is unsolved in the overall clinical programme of this triple combination.

In course of the clinical assessment, the CHMP raised several questions that had to be addressed during the procedure:

- Aliskiren's pharmacokinetics (PK) and pharmacodynamics (PD) are greatly influenced by meal. The study protocol disregards the SmPC recommendation to administer aliskiren after a light meal in order to reduce the variability of PK and PD parameters. New additional analyses investigating the correlation between plasma levels of aliskiren and blood pressure reduction, in a subset of patients enrolled in study SAH2302 were submitted to address this issue. Although results from these analyses might suggest that there is no correlation between plasma levels of aliskiren and the extent of blood pressure reduction, the limited number of patients included in the analysis may have negatively impacted on the results and no sound conclusion may be drawn from these results. However, it is recognised that the issue has a minor impact for the indication "substitution therapy", and this particular concern may be considered as resolved.

- The full antihypertensive effect of aliskiren is stable at 6-8 weeks. According to the study protocol, patients were treated with the low dose of each of the three components of the triple combination for 4 weeks, and were then force- titrated upwards to the high dose of the three components and maintained on these doses for another 4 weeks. The forced up-titration after only 4 weeks of treatment would appear to underestimate the efficacy of 150 mg aliskiren, and may potentially overestimate the efficacy of 300 mg aliskiren. To solve this concern, data have been provided to show that a large fraction of the maximum antihypertensive effect is achieved by 4 weeks of continuous treatment. Considering the variability in the patient response to blood pressure lowering agents in the clinical setting, these data confirm that 4 weeks is indeed the minimum period of time that is necessary to wait before considering up-titration of

aliskiren. The incremental blood pressure reduction seen at week 8 compared to week 4 is therefore attributable to the increase in dose.

- In the elderly population, 75 mg aliskiren has effective blood pressure lowering effect in the majority of patients, whereas no difference between the antihypertensive effect of 150 mg aliskiren and 300 mg aliskiren is apparent. Thus, most of elderly subjects in study SAH100A2302 might have been exposed to excessively high doses of aliskiren. Appropriate statements have been included in the Rasitrio SmPC, advising on the recommended aliskiren starting dose and on the limited effect of the increased dose in the elderly patients.

Given the limited number of patients in the age group 65-75 years and > 75 years, and the high percentage of patients with aberrant readings, additional analyses of efficacy data after the exclusion of aberrant readings have been requested by the CHMP in order to support the evaluation of the benefit of Rasitrio in the elderly population. After the exclusion of aberrant BP readings, the triple combination of aliskiren/amlodipine/hydrochlorothiazide still induced a statistically significant greater reduction in msSBP compared to each dual combination therapy group at study endpoints. Importantly, the magnitude of the blood pressure reduction, excluding patients with aberrant readings in the requested analyses is comparable to the one seen in the overall population. However, the results of the additional analyses performed in elderly patients showed that, after exclusion of patients with aberrant BP readings, no statistically significant difference was observed between the triple combination and the aliskiren-amlodipine double-combination in patients with age ≥65 years. Furthermore, the number of patients ≥75 years old was too small to perform a statistical analysis and to allow for definitive conclusions on the comparison among different treatments.

Thus, a warning was requested by the CHMP to be included in the SmPC for the prescriber stating the there is evidence of an increased risk of adverse events related to hypotension in patients over 65 years treated with Rasitrio (please see section Clinical safety). Therefore, particular caution should be exercised when administering Rasitrio in patients over 65 years. Furthermore, the prescriber is also advised that only very limited data are available on the use of Rasitrio in patients aged 75 years or older. The use of Rasitrio in patients ≥75 years should be restricted to patients for whom blood pressure control has been established for the free combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently without accompanying safety concerns, in particular hypotension. Extreme caution, including more frequent monitoring of blood pressure, is recommended.

Given the paucity of data in the elderly population, the CHMP has requested collection of additional efficacy, safety and tolerability data for the triple combination in a sufficient number of elderly subjects. In this regard, it is noted that the Apollo trial started on January 2011. The study will explore whether intensified therapy with aliskiren given with amlodipine or hydrochlorothiazide reduces the risk of cardiovascular events when compared to similar placebo-based treatment regimens and has been included in the Rasitrio Risk Management Plan.

Data on the efficacy of the high dose of the triple combination are confirmed by the results of the long-term uncontrolled study SAH100A2301**,** showing that, in patients with uncomplicated stage 2-3 hypertension, the triple combination of high dose of Rasitrio produced stable (at week 54 endpoint) reduction in msSBP and in msDBP. Similarly to the effects observed in the short-term study, the number of elderly subjects aged ≥75 years (a total of 27 patients) is too small to allow any conclusion on this subgroup of patients. The choice of the high dose of each of the three components of the triple combination in the long-term study SAH100A2301 and the forced titration design gives limited information about efficacy of the triple combination with lower doses of one or two components. However, the lack of information on the long-term BP lowering effect of the lower strengths of the FDC is a minor issue considering that Rasitrio is intended for "substitution therapy".

The originally requested indication was amended on request of the CHMP for reasons of clarity and ease of understanding for the prescriber.

No short-term or long-term data have been submitted on the efficacy and safety of Rasitrio in subjects with essential hypertension and major vascular co-morbidity (myocardial infarction, stroke, hypertensive retinopathy, heart failure NYHA class III & IV, significant heart valve disease, cardiomyopathy or cardiac dysrhythmia). The exclusion of patients with major cardiovascular co-morbidities from Rasitrio clinical trials raises concerns, since in a real life setting, significant number of patients with hypertension and co-morbidities need triple combination of antihypertensive drugs. The lack of data in patients with major cardiovascular co-morbidities has been appropriately reflected in the SmPC. The results of the additional analyses performed show that higher pre-treatment blood pressure,

male gender, black ethnicity, overweight and overweight-associated disorders (metabolic syndrome and diabetes) were weak predictors of the need of the triple combination for adequate hypertension control.

2.5.4. Conclusions on the clinical efficacy

It is concluded that the overall clinical data available for the combination of aliskiren with both amlodipine and hydrochlorothiazide provide sufficient grounds for granting the indication "substitution therapy" in hypertensive adult patients. The efficacy profile of Rasitrio has been confirmed by statistical analyses performed after the exclusion of aberrant BP readings following the GCP inspection. There is, however an extreme caution required when treating patients > 75 years. Patients with co-morbidities are also to be monitored. The limited information on the efficacy of Rasitrio in the elderly and very elderly patients, as well as the lack of efficacy data in patients with co-morbidities is reflected in the SmPC. Long-term (> 1 year) efficacy data for the triple combination will be derived from the Apollo study.

The indication applied for:

> *Treatment of essential hypertension in adults.*
>
> *Rasitrio is indicated as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide, taken either as three single-component formulations or as a dual-component and a single-component formulation, given concurrently, at the same dose level as in the combination.*

Indication granted by the CHMP:

> *Rasitrio is indicated for the treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently at the same dose level as in the combination.*

The originally requested indication was amended on request of the CHMP for reasons of clarity and ease of understanding for the prescriber.

2.6. Clinical safety

The clinical program includes one main pivotal short term study, one long-term study and several supportive studies. The supportive studies submitted initially are not relevant for the applied indication and only limited safety information can be derived from the additional supportive studies submitted during the evaluation procedure. Thus, the assessment will focus only on short-term and long-term data about safety information derived from studies SAH2302 and SAH2301, respectively.
Pivotal Study SAH100A2302 is an 8 week, double-blind, randomised, parallel group, active controlled study to evaluate the efficacy and safety of the combination of aliskiren/amlodipine/hydrochlorothiazide in moderate to severe hypertension.
Study SAH100A2301 is a 28/54-week, open-label, multicenter study to assess the long-term safety and tolerability of the combination of aliskiren/amlodipine/hydrochlorothiazide in moderate to severe hypertension.

Patient exposure

In the short-term study SAH100A2302, the exposure to double-blind study medication was similar for all treatment groups with a mean duration of 55.4 days as detailed in the following table.

Duration of exposure (Days) to double-blind study medication (Safety set)

	Ali/Aml N = 287	Ali/HCTZ N = 297	Aml/HCTZ N = 295	Ali/Aml/HCTZ N = 309	Total N = 1188
n	287	297	295	309	1188
Mean	55.0	55.4	56.1	55.0	55.4
SD	11.30	10.48	8.39	10.71	10.27
Median	56.0	56.0	56.0	56.0	56.0
Min	1.0	1.0	3.0	2.0	1.0
Max	83.0	70.0	84.0	75.0	84.0

SD = standard deviation.

The duration of exposure by time in the long-term study SAH100A2301 is summarised in the table below. In total, 497 patients were treated with aliskiren/amlodipine/hydrochlorothiazide combination for at least 6 months (≥180 days) and 182 patients for at least one year (≥360 days).

Duration of exposure (Days) by interval (Treated population)

Days	Ali/HCTZ 300/12.5 mg alone N=564 n (%)	Ali/Aml/HCTZ 300/5/12.5 mg N=561 n (%)	Ali/Aml/HCTZ 300/10/25 mg N=556 n (%)	All* Ali/Aml/ HCTZ N=561 n (%)	Total N=564 n (%)
≥ 1	564 (100.0)	561 (100.0)	556 (100.0)	561 (100.0)	564 (100.0)
≥ 7	505 (89.5)	498 (88.8)	554 (99.6)	558 (99.5)	562 (99.6)
≥ 14	2 (0.4)	4 (0.7)	551 (99.1)	554 (98.8)	557 (98.8)
≥28	0 (0.0)	0 (0.0)	541 (97.3)	546 (97.3)	551 (97.7)
≥ 42	0 (0.0)	0 (0.0)	532 (95.7)	537 (95.7)	543 (96.3)
≥ 56	0 (0.0)	0 (0.0)	530 (95.3)	530 (94.5)	532 (94.3)
≥ 180	0 (0.0)	0 (0.0)	479 (86.2)	497 (88.6)	501 (88.8)
≥ 270	0 (0.0)	0 (0.0)	201 (36.0)	200 (35.7)	200 (35.5)
≥ 360	0 (0.0)	0 (0.0)	162 (29.3)	182 (32.4)	194 (34.4)

* Includes aliskiren/amlodipine/ HCTZ 300/5/12.5 mg and aliskiren/amlodipine/ HCTZ 300/10/25 mg

Adverse events

In the short-term study SAH100A2302 the triple combination was associated with the highest incidence of AEs (ca 3% higher than double combinations) with approximately 60% of the AEs being of mild degree. However, the severity of AEs was slightly higher in the arm of the triple combination. The below table summarises the most frequently reported AEs in the short-term study; peripheral oedema was the most common AE.

Number (%) of patients with AEs (greater than or equal to 2% in any treatment group) starting in double-blind period by the order of frequency (Safety set)

Preferred term	Ali/Aml N = 287 n (%)	Ali/HCTZ N = 297 n (%)	Aml/HCTZ N = 295 n (%)	Ali/Aml/HCTZ N = 309 n (%)
Any AE	96 (33.4)	96 (32.3)	99 (33.6)	112 (36.2)
Edema peripheral	23 (8.0)	6 (2.0)	12 (4.1)	22 (7.1)
Dizziness	7 (2.4)	10 (3.4)	5 (1.7)	11 (3.6)
Headache	9 (3.1)	12 (4.0)	15 (5.1)	11 (3.6)
Nasopharyngitis	2 (0.7)	6 (2.0)	10 (3.4)	8 (2.6)
Fatigue	1 (0.3)	6 (2.0)	4 (1.4)	6 (1.9)
Cough	4 (1.4)	0 (0.0)	6 (2.0)	1 (0.3)

Preferred terms are sorted in descending frequency, as reported in the Ali/Aml/HCTZ column.

Diarrhoea had the highest incidence in the aliskiren/amlodipine group (1.4%) and the lowest incidence (0.6%) in the aliskiren/amlodipine/hydrochlorothiazide group. No patients discontinued study drug due to diarrhoea in any treatment group.

The incidence of any AE potentially related to hypotension was 4.9% with the triple therapy and 1.7-3.7% with the respective dual therapies. There was no dose dependent increase in frequency with

titration to the triple 300/10/25 mg dose. None of the patients on Rasitrio discontinued from the study due to hypotension related adverse events.

In both the short-term and long-term study dizziness was the most frequently reported adverse event related to hypotension. In the short term Study SAH2302, dizziness was more frequent in patients treated with Rasitrio (3.6%) compared to the overall study population (2.8%). All other adverse events related to hypotension occurred in ≤0.5% of the patients. Analysis of adverse events related to hypotension by age group (older and younger than 65 years of age) shows that dizziness was the most frequent adverse event related to hypotension for both patients, 65 years of age and older and younger than the age of 65 years.

Pre-treatment orthostatic blood pressure changes largely differed among groups (orthostatic change = SBP decrease of at least 20 mmHg or DBP decrease of at least 10 mmHg from sitting to standing). The treatment with the combination did not increase the incidence of orthostatic BP changes with the use of aliskiren/hydrochlorothiazide but increased the incidence of orthostatic BP changes with the use of other combinations (approximately 2- or 3-times).

From the long-term study SAH100A2301, the number of patients and incidence of total and common AEs is summarised in the table below.

Number (percent) of patients with common adverse events (equal or more than 2.0 percent in any group) (Treated population)

Preferred term	Ali/HCTZ 300/12.5 mg alone N=564 n (%)	Ali/Aml/HCTZ 300/5/12.5 mg N=561 n (%)	Ali/Aml/HCTZ 300/10/25 mg N=566 n (%)	All* Ali/Aml/ HCTZ N=561 n (%)	Total N=564 n (%)
Any Adverse events	**57 (10.1)**	**54 (9.6)**	**259 (45.9)**	**275 (49.0)**	**291 (51.6)**
Edema peripheral	1 (0.2)	0 (0.0)	54 (9.4)	52 (9.3)	53 (9.4)
Headache	10 (1.8)	6 (1.1)	16 (2.9)	22 (3.9)	32 (5.7)
Nasopharyngitis	3 (0.5)	2 (0.4)	20 (3.6)	21 (3.7)	23 (4.1)
Bronchitis	2 (0.4)	3 (0.5)	17 (3.1)	20 (3.6)	21 (3.7)
Diarrhea	5 (0.9)	1 (0.2)	11 (2.0)	12 (2.1)	16 (2.8)
Dizziness	5 (0.9)	3 (0.5)	7 (1.3)	10 (1.8)	15 (2.7)
Influenza	0 (0.0)	0 (0.0)	15 (2.7)	15 (2.7)	15 (2.7)
Back pain	0 (0.0)	2 (0.4)	12 (2.2)	13 (2.3)	13 (2.3)
Vertigo	7 (1.2)	2 (0.4)	4 (0.7)	6 (1.1)	13 (2.3)
Upper respiratory tract infection	2 (0.4)	1 (0.2)	9 (1.6)	10 (1.8)	12 (2.1)

Hypotension was reported in 6 patients (1.1%); all enrolled in the Rasitrio arm of study SAH100A2301. Of these, 5 cases (0.9%) were suspected to be drug-related and resulted in discontinuation of the study drug in 4 patients. Dizziness was reported in a total of 15 patients (2.7%), of whom 6 (1.1%) were suspected to be drug-related and resulted in discontinuation in 1 patient. Three cases of syncope, all in the Rasitrio arm, were suspected to be drug-related. All other adverse events related to hypotension occurred in ≤0.5% of the patients. Analysis of adverse events related to hypotension by age group (older and younger than 65 years of age) shows that dizziness was the most frequent AE related to hypotension for both patients 65 years of age and older, and younger than the age of 65 years. In the subgroup of patients ≥65 years of age, the number of adverse events in the Rasitrio group related to hypotension was too small (n=8 in study SAH2301 and n=6 in study SAH2302) to provide any meaningful insights into the seasonal variation for hypotension related adverse events.

Orthostatic blood pressure change (decrease ≥ 20 mmHg in SBP or ≥10 mmHg in DBP when moving from sitting position to standing position) was reported in three patients, it was suspected to be drug-related and resulted in discontinuation in one patient.

In study SPAUS02, the overall incidence of AEs was 40.2% in the dual aliskiren/amlodipine group and 34.2% in the triple combination group aliskiren/amlodipine/hydrochlorothiazide. The most frequently reported AEs were headache (aliskiren/amlodipine, 8.6%; triple combination, 10.9%) and dizziness (aliskiren/amlodipine, 2.9%; triple combination, 4.0%). The limited duration of the study does not expand the previous evidence about long-term efficacy and long-term safety of the triple combination.
In study SPHDE01, the overall incidence of AEs was similar in each treatment phase p 1: 11.8%; phase 2: 9.8%; and extension: 13.1%). The most frequently reported AE in the extension phase was cervicobrachial syndrome (2 patients, 3.3%). All other AEs in the extension phase occurred in 1 patient

each and there were no reports of events potentially related to hypotension. The proportion of patients with suspected drug-related AEs was 4.3% in phase 1, 3.3% in phase 2, and 1.6% in the extension phase.

In study SPADE01, the overall incidence of AEs was similar in each treatment phase (phase 1: 12.9%; phase 2: 10.1%; and extension: 10.8%). No AEs occurred in more than one patient during the extension phase with the triple combination. Dizziness was reported in one patient (1.5%) and was of mild severity. No other AEs potentially related to hypotension were reported. The limited duration of the study weakens the overall conclusions about safety.

Serious adverse event/deaths/other significant events

In the short-term study SAH100A2302 there were no deaths or cases of angioedema reported after randomisation. The incidence of serious adverse events (SAEs) and discontinuations due to AEs was higher in the triple combination group (aliskiren/amlodipine/hydrochlorothiazide) than in other groups as summarised in the following table.

Number (%) of patients with deaths, serious adverse events and adverse events and abnormal laboratory values leading to permanent treatment discontinuations (Safety set)

	Ali/Aml N = 287 n (%)	Ali/HCTZ N = 297 n (%)	Aml/HCTZ N = 295 n (%)	Ali/Aml/HCTZ N = [illegible] n (%)	Total N = 1188 n (%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	3 (1.0)	2 (0.7)	2 (0.7)	6 (1.9)	13 (1.1)
AE discontinuations	7 (2.4)	2 (0.7)	8 (2.7)	11 (3.6)	28 (2.4)
Drug-related AE discontinuations	5 (1.7)	1 (0.3)	6 (2.0)	4 (1.3)	16 (1.4)
SAE discontinuations	1 (0.4)	0 (0.0)	1 (0.3)	4 (1.3)	6 (0.5)
Discontinuations for abnormal lab values	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)

The below table shows the data of deaths, serious adverse events and adverse events in the long-term study SAH100A2301. There was no death, there were 30 drug-related AEs leading to discontinuation, 6 of which were defined as severe. The most common AE leading to discontinuation was peripheral oedema (13 patients, 2.3%). Other AEs leading to discontinuation in two or more patients included four cases of hypotension, three cases of tachycardia, two cases each of diarrhoea, erectile dysfunction, and hypokalaemia. In patients receiving the triple combination, a case of cerebrovascular accident, palpitations, renal failure, and thrombocytopenia suspected to be related to the study drug was reported.

Number (percent) of patients with deaths, SAEs, and AEs and abnormal laboratory values leading to permanent discontinuation of study drugs (Treated population)

	Ali/HCTZ 300/12.5 mg alone N=564 n (%)	Ali/Aml/HCTZ 300/5/12.5 mg N=561 n (%)	Ali/Aml/HCTZ 300/10/25 mg N=556 n (%)	All* Ali/Aml/ HCTZ N=561 n (%)	Total N=564 n (%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	1 (0.2)	14 (2.5)	15 (2.7)	15 (2.7)
AE discontinuations**	3 (0.5)	5 (0.9)	32 (5.8)	36 (6.4)	39 (6.9)
drug-related AE discontinuations	2 (0.4)	4 (0.7)	25 (4.5)	28 (5.0)	30 (5.3)
SAE discontinuations	0 (0.0)	0 (0.0)	6 (1.1)	6 (1.1)	6 (1.1)
Discontinuations for abnormal lab values	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Includes aliskiren/amlodipine/ HCTZ 300/5/12.5 mg and aliskiren/amlodipine/ HCTZ 300/10/25 mg

Angioedema or other major immunological events were not reported in any group during short-term and long-term study.

Laboratory findings

In the short-term study SAH100A3202, changes in haematology values were small (≤2 g/L in blood haemoglobin). Incidence of notable changes in haematology parameters was very small and without significant differences between aliskiren/amlodipine/hydrochlorothiazide group and the double combination groups. Hyperkalaemia incidence ranged from 0.7% to 3.0%. The incidence of serum potassium <3.5 mmol/L was higher in treatment groups containing hydrochlorothiazide but lower in treatment groups containing aliskiren, in line with the fact that hydrochlorothiazide and aliskiren might have balancing effects on potassium levels. Shifts in creatinine values from normal to high were approximately 2-times more frequent in the aliskiren/hydrochlorothiazide and aliskiren/amlodipine/ hydrochlorothiazide groups (8.5% and 8.3%, respectively) than in the aliskiren/amlodipine and amlodipine/hydrochlorothiazide group (4.6% and 5.1%, respectively). Shifts from normal to high uric acid levels occurred in more patients in the aliskiren/hydrochlorothiazide group (12.1%) than in the other groups, suggesting that the effect was likely driven by hydrochlorothiazide. No patient in the triple combination group discontinued from the study prematurely due to laboratory abnormalities.

Percentage of patients with specified criteria in selected labs by laboratory parameter and treatment group (Safety set)

Laboratory test	Criterion		Ali/Aml N = 287		Ali/HCTZ N = 297		Aml/HCTZ N = 295		Ali/Aml/HCTZ N = 309	
			n	%	n	%	n	%	n	%
Potassium	≥ 6 mmol/L	Total no.	280	100	293	100	294	100	300	100
		No of patients meeting criterion	1	0.4	0	0.0	3	1.0	3	1.0
		High (#)	1	0.4	0	0.0	3	1.0	3	1.0
	> 5.5 mmol/L	Total no.	280	100	293	100	294	100	300	100
		No of patients meeting criterion	2	0.7	2	0.7	6	2.0	9	3.0
		High (#)	2	0.7	2	0.7	6	2.0	9	3.0
	< 3.5 mmol/L	Total no.	280	100	293	100	294	100	300	100
		No of patients meeting criterion	6	2.1	13	4.4	56	19.0	33	11.0
		Low (#)	6	2.1	13	4.4	56	19.0	33	11.0
Creatinine	> 176.8 µmol/L	Total no.	280	100	293	100	294	100	300	100
		No of patients meeting criterion	0	0.0	0	0.0	0	0.0	0	0.0
Blood urea nitrogen	> 14.28 mmol/L	Total no.	280	100	293	100	294	100	300	100
		No of patients meeting criterion	0	0.0	2	0.7	0	0.0	0	0.0
		High (#)	0	0.0	2	0.7	0	0.0	0	0.0

A further classification of patients who meet the specified criterion with respect to laboratory normal ranges. It indicates that the extreme (highest/lowest) post-baseline test value was either above, below, or within the normal range.

In the long-term study SAH100A3201, shifts from normal to low for haemoglobin occurred in 2.8% of patients. Shifts from normal baseline to high post-baseline values were noted for BUN (7.8%), creatinine (12.8%), fasting glucose (9.1%), ALT/SGPT (8.2%), creatine kinase (10.9%), and uric acid (9.3%). Shifts in potassium from a normal baseline to low post-baseline values were reported in 11.4% of patients.

Safety in special populations

No data have been submitted on the efficacy and safety of Rasitrio in subjects with essential hypertension and vascular co-morbidity (myocardial infarction, stroke, hypertensive retinopathy, heart failure NYHA class III & IV, significant heart valve disease, cardiomyopathy or cardiac dysrhythmia), in subjects with hypertensive crisis and/or hypertensive encephalopathy, in subjects with secondary hypertension, in subjects with moderate to severe renal dysfunction or renal replacement therapy. Only very limited data are available in elderly ≥ 75 years old and thus, appropriate request for caution is needed.

There is also no convincing clinical experience with the use of amlodipine in pregnancy. Hydrochlorthiazide crosses placenta. Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with foetal or neonatal thrombocytopenia, and may be associated

with other adverse reactions that have occurred in adults. As a result, Rasitrio is contraindicated for use in second and third trimesters of pregnancy and during breast-feeding, as stated in the SmPC. Further warnings regarding the use in pregnancy are also introduced.

Safety related to drug-drug interactions and other interactions

No safety interactions between the individual monocomponents of Rasitrio have been reported.

Discontinuation due to adverse events

Discontinuation of treatment due to AEs was more incident with the triple combination than with the double combinations in the short-term study SAH100A3202 (3.6% *vs* 1.9%) and increased up to 6.4% in the uncontrolled long-term study SAH100A3201. The most common cause of drug-related discontinuation was peripheral oedema, an AE which is secondary to the use of amlodipine.

Post marketing experience

The fixed combination of aliskiren/amlodipine/hydrochlorothiazide was not marketed in any country at the time of the first MAA submission for Rasitrio in May 2010. Aliskiren, amlodipine and hydrochlorothiazide are currently approved in several EU countries worldwide either as monotherapy or as free combination. A search (cut off date 26-Nov-2009) was conducted in the applicant's safety database for all spontaneous reports and serious solicited (clinical study and post marketing surveillance) reports with concurrent use of aliskiren, amlodipine and hydrochlorothiazide (as single active ingredient or in combination products) revealed 119 cases reporting 427 events. The most frequently reported events (preferred terms reported more than 3 times in total; if an event occurred more than once in the same patients it was counted once) are presented in the table below. These events are either known to be associated with the use of amlodipine and/or aliskiren and/or hydrochlorothiazide or related to the underlying disease. Therefore, review of these cases did not result in any new or additional safety findings.

Post-marketing Adverse Events

MedDRA system organ class	MedDRA preferred term	CS	PMS	SR	Total	Serious events
Cardiac disorders	Atrial fibrillation	2	1	2	5	5
	Palpitations	4		3	7	7
Gastrointestinal disorders	Diarrhoea	1		8	9	3
	Nausea	1	1	2	4	1
General disorders and administration site conditions	Asthenia	2		2	4	3
	Chest discomfort	2		3	5	4
	Chest pain	6	1		7	6
	Concomitant disease progression	5			5	5
	Disease progression	6			6	6
	Drug ineffective	4		2	6	3
	Fatigue	1		6	7	1
	Malaise	1	1	3	5	4
	Oedema peripheral	2		3	5	0
Investigations	Blood creatinine increased		1	6	7	
	Blood pressure increased		4	3	7	5
	Heart rate increased	1		3	4	4
Metabolism and nutrition disorders	Dehydration	1		3	4	3
Nervous system disorders	Dizziness	4	1	6	11	7
	Headache	3	2	3	8	5
	Paraesthesia	2		2	4	2
Respiratory, thoracic and mediastinal disorders Total	Cough	1		4	5	3
	Dyspnoea	6		4	11	10
Skin and subcutaneous tissue disorders Total	Rash		1	3	4	2
	Urticaria		2	3	5	3
Vascular disorders	Blood pressure inadequately controlled	1		3	4	2
	Hypertension	3		1	4	3
	Hypotension	3	1	5	9	7

CT=clinical study report, PMS=post marketing surveillance report, SR=spontaneous report

2.6.1. Discussion on clinical safety

Study SAH2302 and SHA2301 provide the safety data requested by current CHMP guidelines for exposure of patients to short-term treatment and to long-term treatment, 8-week and 6-month/1-year respectively. However, the lack of compliance to the SmPC warning that aliskiren should be taken after a light meal is evident in both studies and thus, limits the interpretation of safety data and hampers their translation to the clinical setting.

In the short-term study SAH100A3202, the triple combination was associated with approximately 3% higher incidence of AEs as compared to double combinations (~36% vs ~33%). Peripheral oedema was the most common AE, followed by dizziness and headache, nasopharyngitis and fatigue. Hydrochlorothiazide did not reduce the incidence of peripheral oedema (aliskiren/amlodipine *vs* aliskiren/amlodipine/hydrochlorothiazide=8.0% *vs* 7.1%). Diarrhoea had the highest incidence in the aliskiren/amlodipine group (1.4%) and the lowest incidence (0.6%) in the aliskiren/amlodipine/hydrochlorothiazide group. No patients discontinued study drug due to diarrhoea in any treatment group. The incidence of hypotension-related AEs in the short term Study SAH2302 was at least 32% higher with the Rasitrio than with the dual therapies. For this set of AEs, the difference in the incidence of hypotension-related AEs between Rasitrio and the dual therapies rose up to 89% in patients aged ≥65 years (10.2% *vs* 5.4%). A specific warning advising caution in the population of elderly >65 years old is present in the SmPC.

No data have been submitted on the safety of Rasitrio in subjects with essential hypertension and major vascular co-morbidity (myocardial infarction, stroke, hypertensive retinopathy, heart failure

NYHA class III & IV, significant heart valve disease, cardiomyopathy or cardiac dysrhythmia) and this limits the drug's comprehensive evaluation of safety. Furthermore, the exclusion of patients with major CV co-morbidities from Rasitrio clinical trials raises concerns, as a significant number of patients with hypertension and CV co-morbidities need triple combination of antihypertensive drugs. The lack of data in patients with major CV co-morbidities has been appropriately reflected in the SmPC.

In the long-term study SAH100A3201, the incidence of AEs was approximately 50%. Peripheral oedema was most common, followed by headache, nasopharyngitis, bronchitis, diarrhoea, dizziness and influenza. The incidence of hypotension-related AEs is, quite surprisingly, not extensively high in the present set.

No deaths, angioedema or other major immunological disorders were reported after randomisation. The incidence of SAEs in the short-term study was higher in the triple combination group than in double combinations (~2% *vs* ~1%) and increased to ~3% in the long-term study. The incidence of discontinuations due to AEs in the short-term study was higher in the triple combination group than in double combinations and increased to ~7% in the long-term study. The most common AE leading to discontinuation was peripheral oedema. Cerebrovascular accident, palpitations, renal failure, and thrombocytopenia were suspected to be related to the study drug in patients receiving Rasitrio. Overall, safety results do not indicate the need of any additional warning, with the exception of symptomatic hypotension, for the triple combination in comparison with the dual combination aliskiren/amlodipine.

The incidence of notable changes in lab parameters exceeded 2% for hyperkalaemia with the triple combination and for hypokalemia in the arms with and without hydrochlorothiazide of the short term study SAH100A3202. In patients receiving hydrochlorothiazide, the incidence of hypokalaemia was lower with aliskiren than without aliskiren. Shifts in creatinine values from normal to high were approximately 2-times more frequent in the aliskiren/hydrochlorothiazide and aliskiren/amlodipine/ hydrochlorothiazide groups than in the aliskiren/amlodipine and amlodipine/hydrochlorothiazide groups. Shifts from normal to high uric acid levels were driven by the presence of hydrochlorothiazide. No patient in the aliskiren/amlodipine/hydrochlorothiazide group discontinued from the study due to laboratory abnormalities.
In the long-term study, shifts from normal to low for haemoglobin occurred in ~3% of patients. Incidence of shifts from normal baseline to high post-baseline values was ~8% for BUN, ~13% for creatinine, and ~8-10% for ALT/SGPT, creatine kinase, uric acid, and fasting glucose. It is known that thiazide therapy may impair glucose tolerance, and dose adjustment of insulin or oral hypoglycemic medicinal products may be required. It is also known that overt diabetes mellitus may occur during thiazide therapy and indeed the submitted data seem to indicate that impairment of glucose tolerance is present following the Rasitrio administration. The lack of information on the need of dose adjustment of antidiabetic drug(s) in diabetic patients treated with Rasitrio is included in the warnings' section of the Rasitrio SmPC. Overall, laboratory changes are in accordance with previous evidence for the three monocomponents. No interaction among the three components was reported.
From the safety database, all adverse reactions reported in clinical trials and post-marketing experience with the mono components or the marketed double combinations have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of the FDC in the adult population has been adequately established in the programme of several clinical studies but relies mainly on the data obtained from the short-term and 1-year-treatment clinical trials SAH100A3202 and SAH100A3201, respectively. The main concern highlighted with the use of the triple combination of Rasitrio is the increase in hypotension-related events. There is evidence of an increased risk of adverse events related to hypotension in patients over 65 years treated with Rasitrio. In addition, only limited clinical data are available from the population of patients $\geq$75 years old. Therefore a specific warning about the use of Rasitrio in the elderly highlighting that extreme caution is recommended when administering the drug to patients $\geq$75 years old was included in the SmPC on request of the CHMP. Additional long-term safety data in the elderly population will be collected in the context of the ongoing Apollo trial. No data are available on the safety of Rasitrio in patients with major CV co-morbidities and the lack of this information has been adequately reflected in the SmPC. Similarly, information on the potential need of dose adjustment of antidiabetic drug(s) in diabetic patients treated with Rasitrio is mentioned in the SmPC.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan

Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risks		
Hypotension	Routine pharmacovigilance activities.	SmPC Caution is advised in elderly patients in section 4.2. There is evidence of an increased risk of adverse events related to hypotension in patients over 65 years treated with Rasitrio. Therefore, particular caution should be exercised. The use of Rasitrio in patients ≥75 years should be restricted to patients for whom blood pressure control has been established for the free combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently without accompanying safety concerns, in particular hypotension (see sections 4.4, 4.8, 5.1 and 5.2). Contraindicated in patients with severe hypotension (Section 4.3): Special warnings and precautions for use (Section 4.4): Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide. Particular caution should be exercised when administering Rasitrio in patients over 65 years. Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide. Elderly patients, over 65 years old, are more susceptible to hypotension-related adverse

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		reactions following treatment with Rasitrio (see sections 4.2, 4.8, 5.1 and 5.2). Elderly, Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide. Elderly patients, over 65 years old, are more susceptible to hypotension-related adverse reactions following treatment with Rasitrio (see sections 4.2, 4.8, 5.1 and 5.2). Listed in section 4.8 Undesirable effects. Hypotension is most likely manifestation of overdose (section 4.9) Risk of hypotension also mentioned in section 5.1, in particular for elderly patients
Dizziness	Routine pharmacovigilance activities.	SmPC Effects on ability to drive and use machines (Section 4.7): No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or using machines it must be borne in mind that dizziness or drowsiness may occasionally occur when taking Rasitrio. Listed in Undesirable effects (Section 4.8):
Peripheral edema	Routine pharmacovigilance activities.	SmPC Listed in section 4.8 Undesirable effects
Diarrhea	Routine pharmacovigilance activities. Study SPP100A2337.	SmPCSpecial warnings and precautions for use (Section 4.4): In the event of severe and persistent diarrhoea, aliskiren/amlodipine therapy should be stopped. Listed in section 4. 8 Undesirable Effects
Rash	Routine pharmacovigilance activities.	SmPC Listed in section 4.8 Undesirable Effects.
Angioedema	Routine pharmacovigilance activities. Study SPP100A2337.	SmPC Contraindication in patients with history of angioedema with aliskiren and in patients with hereditary or idiopathic angioedema (Section 4.3). Special warnings and precautions for use (Section 4.4): As with other medicinal products acting on

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		the renin-angiotensin-aldosterone system (RAAS), angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat, and/or tongue) have been reported in patients treated with aliskiren. A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicinal product that can cause angioedema, including RAAS blockers [angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)] (See section 4.8). Patients with history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren (see sections 4.3 and 4.8). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment (see section 4.8) especially at the beginning of the treatment. If angioedema occurs, Rasitrio 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 maintain patent airways should be provided. Listed in section 4.8 Undesirable Effects Skin and subcutaneous tissue disorders: Angioedema: Rare.
Hyperkalemia	Routine pharmacovigilance activities. Study SPP100A2337.	SmPC Special warnings and precautions for use (Section 4.4) and Interaction with other medicinal products and other forms of interaction (Section 4.5): 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. Caution is advised when co-administered with agents which increase potassium levels. Listed in 4.8 Undesirable effects As with any medicinal product acting on the RAAS, routine monitoring of electrolytes and renal function is indicated in patients with diabetes mellitus, kidney disease, or heart failure (section 4.8).

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Renal dysfunction including blood creatinine increased	Routine pharmacovigilance activities.	SmPC Posology and method of administration (Section 4.2): Rasitrio is contraindicated for use in patients with severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2) (see sections 4.3 and 5.2). No adjustment of the initial dose is required for patients with mild to moderate renal impairment **(**estimated GFR 89-60 ml/min and 59-30 ml/min, respectively) Contraindication (Section 4.3) Severe renal impairment (GFR < 30 ml/min/1.73 m^2). Special warnings and precautions for use (Section 4.4): Caution should be exercised in hypertensive patients with severe renal impairment due to the absence of safety information for Rasitrio in this patient population. As for other medicinal products acting on the RAAS, caution should be exercised when Rasitrio is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolemia (e.g. due to blood loss, severe or prolonged diarrhea, 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. There is no experience regarding the administration of Rasitrio in patients who have recently undergone kidney transplantation, therefore caution should be exercised in these patients. Renal artery stenosis No controlled clinical data are available on the use of Rasitrio in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, as with other medicinal products acting on the renin-angiotensin-aldosterone system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued. Interaction with other medicinal products and other forms of interaction (Section 4.5) Combination of Rasitrio with an NSAID requires caution, especially in elderly patients. Listed in section 4.8 Undesirable effects
Hypokalemia	Routine pharmacovigilance activities.	SmPC Contraindications (Section 4.3): Refractory hypokalaemia. Special warnings and precautions for use (Section 4.4): Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalaemia, hyponatraemia, hypochloraemic alkalosis, hypercalcaemia and hypomagnesaemia). Warning signs of fluid or electrolyte imbalance are dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea or vomiting (see section 4.8). As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals. Hypokalaemia may develop with the use of thiazide diuretics. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH) (see sections 4.5 and 4.8). Interaction with other medicinal products and other forms of interaction (Section 4.5): *Medicinal products affecting potassium*: The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of aliskiren. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium, corticosteroids, ACTH,

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		salicylic acid derivatives). Undesirable effects (Section 4.8): Investigations Not known: Hypokalemia.
Cough	Routine pharmacovigilance activities.	SmPC Description of clinical trial data in section 5.1
Interaction with NSAIDs	Routine pharmacovigilance activities.	SmPC: Interaction with other medicinal products and other forms of interaction (Section 4.5): As with other medicinal products acting on the renin-angiotensin-aldosterone system, NSAIDs may reduce the antihypertensive 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.
Decrease in furosemide systemic levels	Routine pharmacovigilance activities. Study SPP100A2255.	SmPC Interaction with other medicinal products and other forms of interaction (Section 4.5): When aliskiren was co-administered with furosemide, the AUC and C_{max} of furosemide were reduced by 28% and 49%, respectively. It is therefore recommended to monitor the effects when initiating and adjusting furosemide therapy to avoid possible under-utilization in clinical situations of volume overload.
Increased aliskiren systemic levels with the potent Pgp inhibitor, Ciclosporin A and itraconazole	Routine pharmacovigilance activities.	SmPC Contraindication (Section 4.3) and interaction (Section 4.5) The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent Pgp inhibitors, and other potent P-gp inhibitors is contraindicated.
Increased aliskiren systemic levels with moderate Pgp inhibitors, ketoconazole and verapamil	Routine pharmacovigilance activities.	SmPC Contraindications (Section 4.3): The concomitant use of aliskiren with other potent P-gp inhibitors (e.g. quinidine), is contraindicated (see section 4.5). Special warnings and precautions for use (Section 4.4) Caution should be exercised when aliskiren is administered with moderate P-gp inhibitors such as ketoconazole or verapamil. Interaction with other medicinal products and

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		other forms of interaction (Section 4.5): Concomitant use of aliskiren and P-gp potent inhibitors is contraindicated. Moderate Pgp inhibitors Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in plasma levels of aliskirenAUC, respectively. 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 or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone). With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and with diltiazem in elderly patients, the plasma concentration of amlodipine increased by 22% and 50%, respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.
Decreased aliskiren systemic level with grapefruit juice.	Routine pharmacovigilance activities.	SmPC Posology and method of administration (Section 4.2): Grapefruit juice should not be taken together with Rasitrio. Interaction with other medicinal products and other forms of interaction (Section 4.5): Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and Cmax of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with Rasitrio. *Organic anion transporting polypeptide (OATP) inhibitors:* Preclinical studies indicate that aliskiren might be a substrate of organic anion transporting polypeptides. Therefore, the potential exists for interactions between OATP inhibitors and aliskiren when administered concomitantly (see interaction with Grapefruit juice).
Interaction with food	Routine pharmacovigilance activities.	SmPC Posology and method of administration (Section 4.2): Rasitrio should be taken with a light meal. Interaction with other medicinal products and other forms of interaction (section 4.5) Food interactions Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially.
Important potential risks		
Colorectal hyperplasia	Routine pharmacovigilance activities. Study SPP100A2337.	SmPC Listed in section 5.3 preclinical safety data.
Ischemic colitis	Routine pharmacovigilance activities. Newly reported cases potentially describing ischemic colitis will be systematically adjudicated by an external expert panel after pre-selection by the responsible Novartis safety physician.	SmPC No risk minimization activity is currently required
Increased aliskiren systemic levels with other moderate (clarithromycin, telithromycin, erythromycin, amiodarone) or potent Pgp inhibitors (quinidine)	Routine pharmacovigilance activities.	SmPC Contraindication (Section 4.3): The concomitant use of aliskiren with other potent P-gp inhibitors (quinidine), is contraindicated. Interaction with other medicinal products and other forms of interaction (Section 4.5): Caution should be exercised when aliskiren is administered with other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).
Important missing information		
Pregnancy and lactation	Routine pharmacovigilance activities.	SmPC Contraindications (Section 4.3)

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		Second and third trimesters of pregnancy, breast-feeding Fertility, pregnancy and lactation (Section 4.6): Women of child-bearing potential/contraception in males and females: Healthcare professionals prescribing Rasitrio should counsel women of childbearing potential about the potential risk during pregnancy. A switch to a suitable alternative antihypertensive treatment should be carried out in advance of a planned pregnancy since Rasitrio should not be used in women planning to become pregnant. Pregnancy: Rasitrio should not be used during the first trimester of pregnancy. Rasitrio is contraindicated during the second and third trimesters (see section 4.3). If pregnancy is detected during therapy, Rasitrio should be discontinued accordingly as soon as possible. Breast-feeding: It is unknown whether aliskiren and/or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats. Since there is insufficient/limited information on the excretion of aliskiren and amlodipine in human or animal breast milk, a risk to the newborns/infants cannot be excluded. It is therefore not advisable for women who are breast-feeding to use Rasitrio. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Rasitrio therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Paediatric patients	Routine pharmacovigilance activities.	SmPC Posology (Section 4.2): Paediatric population: The safety and efficacy of Rasitrio in children and adolescents below age 18 have not been established. No data are available.
Severe renal dysfunction	Routine pharmacovigilance activities.	SmPC Posology and method of administration (Section 4.2): Rasitrio is contraindicated for use in patients

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		with severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2) (see sections 4.3 and 5.2). No adjustment of the initial dose is required for patients with mild to moderate renal impairment **(**estimated GFR 89-60 ml/min and 59-30 ml/min, respectively). Contraindication (Section 4.3) Severe renal impairment Special warnings and precautions for use (Section 4.4): Renal impairment Caution should be exercised in hypertensive patients with severe renal impairment due to the absence of safety information for Rasitrio in this patient population. Undesirable effects (Section 4.8): Renal and urinary disorders Uncommon: Acute renal failure, renal impairment Not known: renal dysfunction In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk. There have also been reports of peripheral edema and increase in blood creatinine (frequency not known).
Reno-vascular hypertension	Routine pharmacovigilance activities.	SmPC Special warnings and precautions for use (Section 4.4): Caution should be exercised in hypertensive patients with severe renal impairment due to the absence of safety information for aliskiren in this patient population.
Cardiovascular morbidity and mortality reduction	Routine pharmacovigilance activities. Study SPP100A2337. Study SPP100A2340E1.	SmPC Listed in section 5.1 Pharmacodynamic properties.
Serious gastrointestinal disorders	Routine pharmacovigilance activities.	SmPC None.
Hepatic impairment	Routine pharmacovigilance activities.	SmPC Posology and method of administration (Section 4.2), Contraindications (Section 4.3), Special warnings and precautions for use (Section 4.4) In patients with severe hepatic impairment, Rasitrio is contraindicated due to the hydrochlorothiazide component. In patients with mild to moderate hepatic impairment, caution should be exercised when administering Rasitrio due to amlodipine and hydrochlorothiazide component.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Very elderly patients (>75 y/o)	Routine pharmacovigilance activities. Study CSPP100G2301 (APOLLO)	SmPC Posology and method of administration (Section 4.2), Special warnings and precautions for use (Section 4.4), Undesirable effects (Section 4.8), Pharmacodynamic properties (section 5.1) Pharmacokinetic properties (Section 5.2): No data are available on systemic exposure after administration of Rasitrio in elderly patients. When administered alone, the AUC of aliskiren in elderly subjects (>65 years) is 50% higher than in young subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Risk of adverse events related to hypotension in is increased in patients over 65 years treated with Rasitrio. Therefore particular caution is recommended when administering Rasitrio to patients aged over 65 years, and extreme caution in patients aged 75 years or older (see sections 4.2, 4.4, 4.8 and 5.1).
Interaction with clopidogrel	Routine pharmacovigilance activities.	SmPC None.

Several studies are ongoing from the original marketing authorisation for aliskiren. These are included in the pharmacovigilance plan for Rasitrio since they will provide safety information relevant to this product.

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Reduction of blood pressure to the recommended targets has been shown to lower cardiovascular and cerebrovascular morbidity: most patients need more than one drug to reach the desired blood pressure. Rasitrio is intended for substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide, either as three single-component formulations or as a dual-component and a single-component formulation, given concurrently, at the same dose level as in the combination.

The bioequivalence program confirming the BE of the Rasitrio final market image formulation to the EU reference products under light meal conditions, and to the clinical formulation used in the pivotal studies in fasted conditions has been performed. In conclusion, the investigated strengths of the final

market Rasitrio formulation were bioequivalent to the free combination of the EU reference products when administered with a light meal. It was also demonstrated that Rasitrio induces statistically significant greater reduction of systolic and diastolic blood pressure than the component dual therapies in adult patients. The majority of patients achieved blood pressure control defined as msSBP <140 mmHg and msDBP<90 mmHg in the triple combination group and the blood pressure control rate with the triple combination at week 8 endpoint of the treatment was statistically greater than each of the respective dual-combination groups. After exclusion of aberrant blood pressure readings (see 2.5.1), the triple combination of aliskiren/amlodipine/hydrochlorothiazide still induced a statistically significant greater reduction in msSBP compared with each dual combination therapy group at study endpoints. Importantly, the magnitude of the blood pressure reduction, excluding patients with aberrant readings is comparable to the one seen in the overall population.

Furthermore, the once-daily dosing of a combination tablet may lead to improved compliance compared to the free combination of the monotherapies.

Uncertainty in the knowledge about the beneficial effects

Overall, a higher percentage of patients achieved lower BP targets (<130/80 mmHg) in the triple combination arm compared to the dual-combination treatments. However, no data from the patient population at risk of cardiovascular events are available for the use of the triple combination. The lack of information in patients with co-morbidities is, nevertheless, reflected in the relevant sections of the SmPC. The patients who could benefit most from aliskiren/amlodipine/hydrochlorothiazide combination have not been fully characterised, but higher pre-treatment blood pressure, male gender, black ethnicity, overweight and overweight-associated disorders (metabolic syndrome and diabetes) are weak predictors of the need of the triple combination for adequate hypertension control. The efficacy and safety of Rasitrio has not been established in subjects with essential hypertension and vascular co-morbidity (myocardial infarction, stroke, hypertensive retinopathy, heart failure NYHA class III & IV, significant heart valve disease, cardiomyopathy or cardiac dysrhythmia). This information is correctly included in the SmPC. It is to be noted that the long-term (beyond 1 year) ability of Rasitrio to sustain an antihypertensive effect has not been established and will be addressed in the future.

The clinical development programme for Rasitrio was conducted without attention to the fact that food is known to affect the bioavailability of aliskiren and data were not collected to assess the timing of Rasitrio administration in relation to food. Study results are also confounded by the fact that aliskiren was administered not after a light meal as per the approved SmPC. Additional analyses investigating the correlation between plasma levels of aliskiren and blood pressure reduction in a subset of patients enrolled in study SAH100A2302 were hampered by the limited number of patients and a sound conclusion on the existence of a correlation between aliskiren plasma levels and blood pressure reduction was therefore not possible. However, this issue is not of a major importance for the applied tindication for "substitution therapy" of the triple combination.

The minimally effective dose of the combination in the elderly has not been convincingly demonstrated. Evidence of the BP lowering effect of 75 mg aliskiren in the elderly has been included in the Rasitrio SmPC together with information on the recommended starting dose of aliskiren in elderly patients. The limited number of elderly subjects in the pivotal trials assessing the efficacy and safety of aliskiren-containing products is a major problem of the development programme of aliskiren and aliskiren containing products. The SmPC includes appropriate wording that Rasitrio is to be used with extreme caution in patients aged 75 years or older. Further data will be collected the framework of Apollo clinical trial.

The original claim that once-daily dosing of a combination tablet may lead to improved compliance compared to the free combination of the monotherapies or the dual combination plus the monotherapy, remain to be demonstrated.

Risks

Unfavourable effects

Treatment with Rasitrio may result in an increased incidence of angioedema. Furthermore, the use of Rasitrio may increase the risk of hypotension-related events. This is of particular concern for the elderly population. Both risks are reflected in the relevant sections of the SmPC for this product.

In line with the other approved aliskiren containing medicinal products (Rasilez and Rasilez HCT), there is a warning in the SmPC of Rasitrio to avoid administration of the FDC in patients at risk for gastro-intestinal side effects, specifically diarrhoea.

A signal for aliskiren-induced toxic epidermic necrolysis was detected during the postmarketing use of aliskiren. These events will be closely monitored. Furthermore, in the postmarketing settings, cases of colorectal hyperplasia and colon cancer with aliskiren were identified and there is a concern that the presence of aliskiren in the fixed dose combination may increase the relative risk for solid tumours. The RMP addresses this potential carcinogenic concern.

Data on the use of Rasitrio in children and adolescents below 18 years, pregnant or nursing females are not available. This information is adequately captured in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

Long-term safety data from clinical trials are available only for one year-long treatment. Long-term efficacy and safety data will be collected in the framework of the Apollo clinical trial.

The biological mechanisms underlying the increased risk of angioedema due to the presence of aliskiren in the fixed dose combination have not been established.

Benefit-risk balance

Importance of favourable and unfavourable effects

The current CHMP guidelines do not give a definite guidance on the requirements for the claim of "wide therapeutic experience", which is the ground for the substitution indication sought for Rasitrio. Considering overall data from the aliskiren clinical development programme, the cumulative post-marketing data available for aliskiren-containing products, as well as the previous CHMP positive opinion on the benefit/risk of the combinations of aliskiren/amlodipine and aliskiren/hydrochlorothiazide, it is acknowledged that - with the exception of selected sub-populations of patients, including the elderly population and patients with major co-morbidities - the amount of data now available for the combination of aliskiren with both amlodipine and hydrochlorothiazide provide the base for the substitution indication in hypertensive adult patients.

Bioequivalence between the free combination of monocomponents and the fixed dose combination of Rasitrio has been demonstrated. The high number of aberrant BP readings, highlighted during the GCP inspection of 3 centres of the pivotal study SAH100A2302 did not influence the overall efficacy of the combination. In particular, statistical re-analyses of the differences in the blood pressure lowering effect of Rasitrio over the dual combination of aliskiren/amlodipine and aliskiren/hydrochlorothiazide after the exclusion of patients with aberrant BP readings are reassuring of the efficacy of the triple combination when compared to the dual combinations, in the general population. Further efficacy and safety data for patients aged $\geq$ 65 years will be collected in the long-term Apollo trial.

The lack of clinical data for patients aged > 65 years resulted in a specific warning on the elderly in the relevant section of the SmPC, in particular stating that Rasitrio is to be used with extreme caution in patients aged $\geq$ 75 years. There is also a lack of efficacy and safety data in patients with co-morbidities, who represent a significant percentage of the hypertensive population treated with a triple combination of antihypertensive drugs.

Benefit-risk balance

The decrease in blood pressure represents an established factor in lowering the risk for cardio- and cerebrovascular disorders. The majority of patients need more than one drug to achieve the desired blood pressure, making the use of combination of antihypertensive drugs of potential help for a successful blood pressure control. The fixed dose combination of aliskiren/amlodipine/hydrochlorothiazide (150/5/12.5 mg and 300/10/25 mg dose strengths) induces significantly greater reduction of systolic and diastolic blood pressure than the component dual therapies in adult patients without major co-morbidities. Only limited long-term clinical data are available at present. Elderly and very elderly patients are scarcely represented in the study population in which Rasitrio has been studied. In particular, the increase in hypotension and hypotension-related events, observed in the patients $\geq$ 65 years, limits the benefit of the triple combination in this age group. These findings have been reflected in the SmPC. The CHMP recommended strong cautionary statements for the use of Rasitrio in patients $\geq$65 years old, including a specific warning that extreme caution is recommended when administering the drug to patients $\geq$75 years old. An official commitment to provide additional long-term efficacy and safety data is included in the RMP.

Discussion on the benefit-risk balance

The overall benefit/risk of Rasitrio is considered positive for the indication: *treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently at the same dose level as in the combination.*

Concerns raised on the paucity of efficacy and safety data in the elderly population are solved by the specific warnings, agreed by the CHMP and included in the SmPC for the use of Rasitrio in patients $\geq$ 65 years and $\geq$ 75 years and as such, the SmPC adequately reflects the benefits and the restrictions or warnings for the use of this medicinal product.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Rasitrio in the treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently at the same dose level as in the combination is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR). In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Obligation to complete post-authorisation measures

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.