EMA/646940/2010

WITHDRAWAL ASSESSMENT REPORT FOR

RASIVAL

International Nonproprietary Name:

Aliskiren+Valsartan

Procedure No. EMEA/H/C/1191

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.
This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for Rasival (aliskiren/valsartan) in the *Treatment of essential hypertension in adults as substitution therapy only in patients already adequately controlled with aliskiren and valsartan, given concurrently, at the same dose level as in the combination*, is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

1. Pharmacokinetic data in a bioequivalence study are intended to provide reassurance regarding equivalence of all facets of a product's effects. The bioequivalence of the fixed combination to the free combination has not been shown in the fed state. It is considered that the in-house study data presented by the applicant do not provide a convincing rationale to waive the requirement for a bioequivalence study in the fed state. Results from the food effect study SPP2110 do not remove the need for a fed bioequivalence trial. A bioequivalence study in the fed state, as described in the proposed SmPC, is required and the applicant should provide the results of such study.

2. There are no data supporting the claim that the PK/PD data of the aliskiren 'light meal' study can be extrapolated to the FDC. The applicant should provide PK and PD data (measurements of PRA and Blood Pressure) of a study investigating the effects of a light meal vs. fasting conditions with the two strength doses (150/160mg and 300/320mg).

3. The Applicant should provide the food effect study (CSPV100A2103) performed with the 150/160 mg aliskiren/valsartan combination and discuss the results with regards to the contribution of aliskiren to the BP lowering effect, taking into account the results of the analysis of the PK-PD relationship reported in the Clinical Overview accompanying the food effect study CSPP100A2110.

4. The positive benefit-risk for each dose of the aliskiren-valsartan combination has not been adequately established in the programme of clinical trials presented. The wide therapeutic experience with the use of this combination has not been shown. The use of the aliskiren/valsartan combination is associated with a higher number of adverse events that are related to the dual blockade of RAS, such as hypotension, syncope, hyperkalaemia and renal dysfunction. These safety issues remain an issue of major concern, in particular in patients at risk for side effects that are related to inhibition of the RAS, such as elderly patients, patients with renal dysfunction, patients with diabetic nephropathy, patient using diuretics and patients with therapy-resistant hypertension. Risk is not well quantified in all of these patient groups. So far, the clinical benefits have not been shown and the add-on effect in patients who do not respond in monotherapy has not been demonstrated. The long term benefit and safety of a fixed dose combination of valsartan and aliskiren inducing dual RAS blockade, that will be almost maximal when the higher dosages are used, has not been established either. Additional efficacy and safety data are needed, including the data from patient groups described above, in order to establish a positive benefit-risk balance.

Inspection issues
None

II. EXECUTIVE SUMMARY

II.1 Problem statement

In August 2009, Novartis Europharm Ltd submitted a Marketing Authorisation Application for Rasival (aliskiren+valsartan) 150/160 mg and 300/320 mg film-coated tablets via centralised procedure. The claimed indication is:

Treatment of essential hypertension in adults.
Rasival is indicated as substitution therapy only in patients already adequately controlled with aliskiren and valsartan, given concurrently, at the same dose level as in the combination.

Hypertension has been identified as a major risk factor for cardiovascular diseases such as stroke, myocardial infarction, and heart failure: it's widely recognised that an adequate control of hypertension is important to significantly decrease cardiovascular mortality and morbidity.
All international guidelines for the management of hypertension recommend a general target blood pressure (BP) < 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. Then the angiotensin converting enzyme (ACE) transforms angiotensin I into the active octapeptide angiotensin II, which acts via type-1 angiotensin II receptors (AT1) to increase arterial tone, adrenal aldosterone secretion, renal sodium reabsorption, sympathetic neurotransmission, and cellular growth.
Some of currently used antihypertensive drugs intervene at different points of 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 many therapeutic choices, in the majority 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 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.

Indeed, the Applicant intends to register aliskiren/valsartan fixed combination at doses of 150/160 mg and 300/320 mg in patients adequately treated with the free combination with the aim to improve patient compliance.

Aliskiren is the first renin-inhibitor authorized in EU via the Centralized Procedure in August 2007. Aliskiren exhibits a new mode of action compared with other drugs acting on the renin-angiotensin system. Aliskiren directly inhibits renin, the enzyme responsible for the production of angiotensin I, blocking the renin system at its very origin. Renin inhibitors like aliskiren do not block renin-like enzymes, such as cathepsin D or tonins, which are present in the vascular wall and which release angiotensin I from angiotensinogen. Renin has a unique specificity for its only known physiological substrate, angiotensinogen. This specific inhibition of the renin system by diminishing renin activity has the advantage to not interfere with other metabolic pathways.

Valsartan is an angiotensin II receptor blocker/antagonist (ARB) that inhibits the interaction of Angiotensin II and its receptor, primarily the AT1 receptor, and therefore blocks the hypertensive and other effects of Angiotensin II. Valsartan was first developed for the treatment of hypertension, and is approved for this indication as monotherapy or in combination with other antihypertensive agents in once daily doses of 80 mg to 320 mg in Europe, the United States, and in many other countries. It has been marketed for hypertension as monotherapy since 1996, in combination with hydrochlorothiazide since 1997, and in combination with amlodipine since 2007. Valsartan has also been approved and marketed for the treatment of patients with chronic heart failure since 2005 and for the treatment of patients with post-myocardial infarction since 2005 in the Mutual Recognition Procedure countries.

II.2 About the product

Rasival is a new fixed combination of two antihypertensive drugs, aliskiren and valsartan for the treatment of essential hypertension in adults as substitution therapy in 150/160 mg and 300/320 mg film-coated tablets.

Aliskiren is an orally, direct and selective inhibitor of human renin, the enzyme responsible for the production of angiotensin I, blocking the renin system at its very origin. It belongs to the pharmacotherapeutic group of "Renin-inhibitors", ATC code: C09XA02.
In EU, aliskiren received marketing authorization via the Centralized Procedure in August 2007, as 150 mg and 300 mg film-coated tablets.

Valsartan is an angiotensin II receptor blocker/antagonist (ARB) that inhibits the interaction of Angiotensin II and its receptor, primarily the AT1 receptor, and therefore blocks the hypertensive and other effects of Angiotensin II. Valsartan was first developed for the treatment of hypertension, and is approved for this indication as monotherapy or in combination with other antihypertensive agents in once daily doses of 80 mg to 320 mg in Europe, the United States, and in many other countries. It has been marketed for hypertension as monotherapy since 1996, in combination with hydrochlorothiazide since 1997, and in combination with amlodipine since 2007. Valsartan has also been approved and marketed for the treatment of patients with chronic heart failure since 2005 and for the treatment of patients with post-myocardial infarction since 2005 in the Mutual Recognition Procedure countries.

The combination of aliskiren and valsartan is expected to achieve an effective inhibition of the RAS by blockade of the AngII receptor and inhibition of the compensatory response in renin activity secondary to the treatment with ARB. Some studies suggest that the simultaneous blockade of the RAS at several levels could induce organ-specific benefits.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

The non clinical development programme is described by the Applicant in a clear, adequate manner. The relatively low number of specific pre-clinical studies included in the Dossier has been adequately discussed by the applicant and it appears to adhere to the EMEA/CHMP/SWP/258498/2005 guideline for reduced use of experimental animals. The marked interaction on valsartan on aliskiren circulating levels observed both in the non-clinical and clinical settings raises the question as to whether the Applicant needs to comply with the EMEA guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95), by carrying out a specific BE study.

The clinical program in this submission aims to prove the efficacy and the safety of the combination of aliskiren/valsartan in the treatment of essential hypertension with the limited indication of "substitution" treatment, that is a combination that the physician can prescribe in hypertensive patients who are already stably controlled by the two drugs.
The doses in the clinical program – low dose combination (LDC) = 150 mg aliskiren+160 mg valsartan; high dose combination (HDC) = 300 mg aliskiren + 320 mg valsartan, were selected on the basis of previous studies and of the current marketed formulations of the two components, not on new dose-response studies.

For analyses on efficacy, the clinical program includes one main new study and two non-new supportive studies. For analyses on safety, the clinical program includes one new long-term main study. See the table below

Overview of studies and their function

Topic	Source of data
Dose selection studies	None
Patients with essential hypertension	
Pivotal efficacy and safety study Short-term (8 weeks) placebo-controlled efficacy and safety study	• **Study CSPP100A2327:** Phase III**,** randomized, double-blind, 4-arm factorial, parallel group, multi-center, placebo controlled dose escalation study; pivotal study.
Pivotal long-term safety study (12 months)	• **Study CSPV100A2301*:** Phase III, 54 week, open-label, multicenter study to assess the long term safety and tolerability of the combination of aliskiren 300 mg/valsartan 320 mg.
Supportive study Short-term (8 weeks) placebo-controlled efficacy and safety study	• **Study CSPP100A2203:** Phase II, randomized, double blind, multifactorial, placebo controlled, parallel group. Designed as a pivotal trial for efficacy and safety of aliskiren monotherapy, and as proof-of-concept trial for the aliskiren/valsartan combination; supportive study.
Patients with essential hypertension not adequately responding to HCTZ 25 mg monotherapy	
Supportive study Short-term (8 weeks) active-controlled efficacy and safety study	• **Study CSPP100A2331, supportive study:** Phase III, double-blind, active-controlled study evaluating the combination of aliskiren/valsartan/HCTZ (300/320/25 mg), aliskiren/HCTZ (300/25 mg), valsartan/HCTZ (320/25 mg), and HCTZ 25 mg.

*In this study, open-label addition of HCTZ was permitted in patients whose BP was not adequately controlled by treatment.

Since the core registration studies were conducted with the free combination of aliskiren and valsartan, a bioequivalence development program was established to bridge the clinical efficacy and safety data obtained with aliskiren and valsartan in free combination to the fixed combination final market image (FMI) tablets.
These studies are summarised in the following table:

Summary of biopharmaceutic studies

Study	Objective	Population		Dosage form	Dose	N
CSPV100A2104	Pilot relative bioavailability	HS	M/F	Aliskiren (FMI) Valsartan (CSF)* Aliskiren/Valsartan (TIC, MG1)	150 mg SD 160 mg SD 150/160 mg SD	36
CSPV100A2111	Definitive Bioequivalence	HS	M/F	Aliskiren (FMI) Valsartan (CSF)* Aliskiren/Valsartan tablet (FMI)	300 mg SD 320 mg SD 300/320 mg SD	84
CSPV100A2114	Food-Effect	HS	M/F	Aliskiren/Valsartan tablet (FMI)	300/320 mg SD	34

HS = Healthy subjects, M = Male, F = Female, SD = Single dose, FMI = Final market image, CSF = Clinical service form, TIC = fixed combination capsule (tablet-in-capsule), MG1 = film-coated bilayer tablet (melt granulation variant 1), *Valsartan CSFs were identical to the EU approved formulations with the minor exception of the colour of capsule shell.

Reference: [Synopses of individual studies] [Tabular listing of all clinical studies]

The assessments of the Rasival dossier refer to several guidelines which are listed below for reasons of clarity.

- 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 MEDICINAL 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 THERAPEUTIC CLASSES IN THE FIELD OF CARDIOVASCULAR TREATMENT AND PREVENTION
- CPMP/EWP/QWP/1401/98: NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOEQUIVALENCE
- CHMP/EWP/240/95 rev1: GUIDELINE OF THE CLINICAL DEVELOPMENT OF FIXED COMBINATION MEDICINAL PRODUCTS

No Scientific Advice was issued by the CHMP, anyway advice was released by National Competent Authorities: The applicant confirms that the clinical development program for aliskiren/valsartan and study designs were discussed with the following National Health Authorities: DK, FR, SE, UK, ES, NL between 2005 and 2007. The applicant acknowledged, during the consultation period, that the choice of dosages was determined by market considerations.
A paediatric development plan is not foreseen. This was agreed with CHMP prior to the application and is therefore acceptable.

II.4 General comments on compliance with GMP, GLP, GCP

GMP
No quality related issues have been identified that necessitate an inspection prior to authorisation.

GLP
Regarding the 2 ALI/VAL non clinical studies performed for the present application, the quality of the data falls in two categories, specifically:

- Full GLP status: study completely in compliance with GLP principles at that time performed and with Quality Assurance signature and documentations included (13wk study)

- No full GLP status: study performed to high standards of scientific quality at that time, however QA did not monitor the study or audit the report (2wk study.)

The 13 wk GLP study (Report No. 0680120) was performed in the period September-December 2006 by Charles River Laboratories Preclinical Service Montreal. For this site EMEA inspection Unit has requested inspections twice in the last three years for other applications. The first inspection was a study audit inspection but the second, performed by the Swedish and Belgian GLP Monitoring Authorities and also included a facility inspection as well. After that Belgian Monitoring Authority released the Statement of GLP compliance C07 dated 24 October 2006 that covers the period in which Report No. 0680120 was performed.
With the responses to D120 LoQ the Applicant's has provided supporting documents which give the necessary assurance that the pivotal 13-week toxicity study in rats (Study 802359) and the 4-week study to qualify impurities (Study 802895) have been conducted and reported in full compliance with GLP requirements.
For these reasons the GLP inspection for this application is not requested.

GCP
The applicant states that all studies were conducted in a multicenter, multi-country setting in full compliance with Good Clinical Practice. All studies were closely monitored by Novartis personnel or a contract organization for compliance to the protocol and the procedures described in it.
The assessment of the clinical documentations did not raise concerns about compliance with GCP. Therefore a GCP inspection is not considered necessary.

II.5 Type of application and other comments on the submitted dossier

This is an application for centralised procedure submitted in accordance with Article 3(2)(a) (Optional scope-New active substance) and with Article 10b of Directive 2001/83/EC, as amended (fixed combination application).
A complete dossier has been submitted, also including a Risk Management Plan and an Environmental Risk Assessment. The results of the readability testing on Package Leaflet have been provided on Day 121, together with the answers to the questions and in line with the updated PL.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

Aliskiren hemifumarate

Aliskiren hemifumarate of Novartis has already been authorized via the centralised procedure both in monotherapy and in a combination product. Information submitted in the original and supplementary documentations were evaluated and accepted by the CHMP.
Aliskiren hemifumarate has four chiral centers, but is obtained as a single diastereoisomer, all S-configured.
Sufficient scientific information has been presented on 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. Nevertheless no conversion was observed in the solid state and no influence of polymorphism on drug dissolution has been proved. Satisfactory identification of the three different forms was performed by X-ray powder spectra, Differential Scanning Calorimetry (DSC) and ThermoGravimetric Analysis (TGA). Aliskiren hemifumarate is very hygroscopic. Addition of synthesis C in alternative to synthesis B has been the object of a type II variation. The introduction of synthesis C had the advantages of reduced

complexity. The addition of an alternate chemical synthetic route has been supported by comparative analytical data and stability data with the drug substance obtained with method B.
For both syntheses the manufacturing process has been fully detailed, including operating conditions, quantities of solvents, reagents, catalysts. Additional information has been provided on the blending step. Adequate in-process controls 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 active substance are all of synthetic origin, therefore do not pose a risk of TSE/BSE contamination.
The structure of aliskiren hemifumarate 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 and X-ray powder diffractometry (XRPD), optical rotation (single diasteroisomer), particle size analysis.
Appropriate specifications have been set up and include appearance, particle size, appearance of the solution, identification (IR, XR and optical rotation), residual solvents (GC), water content, sulphated ash, heavy metals, assay (titration and HPLC), assay of the salt (fumaric acid), microbiological quality. Limits for specified and total impurities are in line with ICH limits and are considered acceptable. Analytical methods have been adequately detailed and validated where necessary. The container closure system chosen assures the required tight packaging, due to the hygroscopicity of the drug substance. Based on the comparative analytical data it is demonstrated that aliskiren hemifumarate drug substance manufactured as per the currently approved synthetic route B and the proposed alternate synthetic route C comply with all specifications of their corresponding testing monographs.
Stability data on pilot and commercial batches from synthesis B have been carried out under ICH long term (24 months, 25°C/60%RH) intermediate and accelerated conditions (6 months, 40°C/75%RH) and 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 twelve and three months, respectively, and a re- test period of 24 months stored not above 25°C in a very tight packaging is requested. Additional stability data on the drug substance manufactured with route B and C have been provided upon request and comprise long term stability data up to 60 and 24 months, for route B and C, respectively, for development batches and 36 and 18 months for route B and C, respectively, for commercial batches. Clarification is required as to what re-test period the applicant is claiming for aliskiren synthesis B and C. Note that the previous ret-test period with the conditions "Do not store above 25 °C" and "Protect from light" was 30 months for route B and 24 months for route C.

Valsartan

Valsartan of Novartis has already been authorized via the centralised procedure both in monotherapy and combination products. Information submitted in the original and supplementary documentations were evaluated and accepted by the CHMP.
Valsartan is a white to practically white, fine powder, melting at 105-110 °C with decomposition. Its solubility is very low in water and in acidic media and increases with increasing pH.
There is one chiral center in the valine moiety of the molecule but the pure (S)-enantiomer is essentially used. No solid-state polymorphism is known to exist for valsartan.The manufacturing route comprises four consecutive synthetic steps and one auxiliary step for reagent preparation. Valsartan is manufactured via a synthetic route introduced years ago. All starting materials are commercially available and are well established, described in detail and controlled by adequate specifications. It is required to specify the actual standard and maximum batch size that is not clearly defined in the dossier. Information requested on on the supplier of compound 10 have been provided.

Valsartan specifications include tests for appearance (visual examination), absorbance (420 nm) and clarity of the solution in methanol, particle size (laser light diffraction), identity (IR, HPLC), R-enantiomer (HPLC), assay based on anhydrous and solvent-free substance (HPLC, titration), residual solvents (GC), water content (KF), sulphated ash, heavy metals (X-ray fluorescence) and Microbial Limit Test (plate count method). Limits for specified and total impurities are in line with ICH limits and are considered acceptable.
Stability data are provided on a significant number of batches. The following parameters were investigated: appearance, assay and related substances, specific rotation in methanol, clarity of solution in methanol, absorbance and water. Valsartan proved very stable and not susceptible to degradation even when stored at elevated conditions of temperature and humidity. All batches complied with the proposed specification at all storage conditions. A retest period of 3 years without special requirements for storage was accepted.

Some additional information requested on the batch size and packaging materials have been provided.

Drug Product

The aim of the formulation development was an immediate release tablet combination product that would be bioequivalent to the marketed products containing each substance individually. The product was developed in two strengths, 150/160 mg and 300/320 mg.
A tablet formulation was developed. The other excipients are commonly used excipients for this pharmaceutical form. A conventional protective film coat, water based, was applied. The composition is dose and weight proportional for the two strengths with minor differences in the coat composition. The final formulation chosen proved to be bioequivalent with the free forms. Comparative dissolution data has been provided and the dissolution profiles have been discussed. No other dissolution data are provided on batches used in clinical trials since it is stated that only mono-products have been used in clinical trials. Further clarification is requested on batches used in clinical trials. The dissolution specifications proposed are acceptable on the basis of the further dissolution data provided but the applicant has committed to revise dissolution specifications for aliskiren as soon as further statistical data will be available.
Additional compatibility studies between the two drug substances have been provided. The compatibility data of the drug substances with the excipients have been updated to take into account the new added excipients. All the excipients comply with pharmacopoeial standards. None of the excipients are of animal or human origin. The dissolution test had been developed based on the experience gained with the free forms.
The dissolution test is used to compare pilot scale and production batches and to support biowaiver between the two strengths. The discriminatory power of the test has been demonstrated on stressed samples.
The manufacture process comprises the following main steps: preparation of valsartan granulate by roller compaction, preparation of aliskiren granulate by granulation, blending, compression and coating. Many mixing and screening steps are foreseen in between. A more detailed description of the manufacturing process has been provided. The operations involved are standard ones. However the granulation is to be considered a critical step. No validation data had been provided and only a summary of the process validation scheme had been provided in section 3.2.R.. Therefore validation data had been requested. Validation data performed on 3 commercial batches for both strengths has now been presented and support process robustness and reproducibility. At present the process is considered as validated.
The specification for SPV100 tablets includes tests for: appearance (visual examination), identification of aliskiren and valsartan (TLC, HPLC), identification of colorants (colour reaction), mean tablet mass, dissolution (HPLC, UV), degradation products of both actives (HPLC); assay for valsartan and aliskiren (HPLC), uniformity of dosage units (Ph. Eur), and microbial limit tests.
The specifications are generally acceptable. The applicant has been asked to add a specification for average mass. The specification for dissolution for aliskiren seems too large; as stated above, The limits for specified impurities justified by toxicological studies performed with *in vitro* genotoxicity assays and rat toxicity studies. The limits for these degradation products at release were not immediately accepted since the impurities are not found at concentration above 0.1% in representative batches. The specifications have now been restricted at release and the applicant is requested to do the same at the shelf life on the basis of stability data.
Stability data are available on both pilot scale and commercial batches in both proposed packaging. Based on the data available (18months at long term conditions and at intermediate conditions and six months at accelerated conditions) the requested shelf life might be granted for the product in blister packs if storage conditions are clarified as requested and in the proposed conditions: "do not store above 30°C; store in the original package in order to protect from moisture".

Discussion on chemical, pharmaceutical and biological aspects

1. In the day 80 AR two major concern had been raised:

   - lack of validation data for the manufacturing process
   - paucity of dissolution data in the pharmaceutical development and to support the biowaiver for the lower strength

In day 120 response document, the applicant has responded satisfactorily:

- validation data on three full scale commercial batches of both 150/160 mg and 300/320 mg strengths according to the validation protocol presented in 3.2.R have been provided, which confirm the reproducibility and robustness of the process.
- dissolution data available on development batches have been presented, dissolution comparison data between the biobatch and three full scale production batches of both strengths have been provided. Similarity is demonstrated in most cases. See below point 3. The dissolution specifications are accepted but the applicant has committed to revise the dissolution specifications for aliskiren hemifumarate as soon as more statistically significant data are available. See the list of outstanding issues.

2. The data submitted fulfil most of the requirements.

3. The only issue remained concerns the dissolution
A commitment is required on dissolution specifications: see also point 1.

Conclusion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. Major requests have been fulfilled. The results of validation study presented indicate satisfactory consistency and uniformity of important product quality characteristics.
It may be concluded that the product has a satisfactory and uniform performance in clinics, provided that the required further dissolution data are definitely re-assuring on bioequivalence.
Some commitments are required, in particular to restrict the dissolution specifications for aliskiren hemifumarate. Some points should be clarified. See the list of outstanding issues.

III.2 Non clinical aspects

Pharmacology
It is postulated that the antagonism of plasma renin may afford further advantages compared to the simple blockade of angiotensin receptors, but no pre-clinical evidence is provided in support of this rationale. Reports from the literature show that short-term renin inhibition by another renin inhibitor, tarlakiren, provides additional BP lowering activity in guinea pigs treated with suboptimal doses of losartan. A chronic 2-week study in SHR confirmed that renin inhibition by aliskiren synergizes with valsartan in reducing BP levels. The association aliskiren/valsartan was also reported to reduce the production of inflammatory markers ICAM-1, VCAM-1 MCP-1 and NO in a synergistic manner compared to the single components given alone, affording protection against atherosclerotic changes. Overall, the available human data are considered as the starting point providing information about the efficacy and safety of aliskiren/valsartan association in man, thus making animal studies unnecessary.

Pharmacokinetics
Pharmacokinetics and disposition of aliskiren and valsartan have been investigated in animals and humans, in vivo and in vitro. The majority of reported data deals with human experiments, indicating poor availability of non-clinical animal data. The most relevant PK finding comes from the study by Vaidyananthan et al., which was conducted in-house by Novartis at various sites in USA and EU. In this study valsartan was found to induce a 26% decrease in aliskiren AUC; such change was statistically significant ($p=0.002$) but was judged by the investigators "not clinically relevant". However, why such statistically significant interaction has no clinical relevance was not explained nor discussed in the original dossier. A point of clarification was therefore raised in the D120 LoQ - Clinical (PK) part. Please refer to the assessment of the clinical part (PK) for the discussion of this issue.

Toxicology
Repeated dose toxicity
Tracheal inflammation/necrosis and premature deaths were previously observed for aliskiren during repeated-dose oral gavage studies in rodents treated at doses ≥ 200 mg/kg/day. The highest dose of 300/300 mg/kg/day (aliskiren/valsartan) selected during the 2- and 13-week rat toxicity studies for the combination was considered to be at, or above, the maximum tolerated for repeated administration

in this species. In the preliminary 2-week rat toxicity study, this high dose was also associated with reduced body weight gain and slightly low food consumption consistent with mild non-specific toxicity. These findings therefore further support the selection of 300/300 mg/kg/day (aliskiren/valsartan) as the highest dose during the subsequent 13-week rat toxicity study.

In the 13-week rat study, microscopic changes included reversible, minimal or slight vacuolization of the squamous epithelium at the limiting ridge of the non-glandular stomach of animals treated at 300/300 mg/kg/day (aliskiren/valsartan). This finding was also present but at a lower incidence, among animals that received 300 mg/kg/day valsartan alone. Other significant changes observed for the combination during this study were consistent with the expected pharmacological actions of one or both components and comprised increased urine volumes and decreased heart weights that may reflect reduced cardiac work associated with lower blood pressure. The NOAEL was considered to be 150/150 mg/kg/day based on the histopathological changes in the stomach at the highest dose.

Reproductive Toxicology
As drugs affecting the Renin-Angiotensin-Aldosterone System are contraindicated in Europe during second and third trimesters of pregnancy, no specific fertility studies were carried out with the aliskiren/valsartan combination. Sections 4.3 and 4.6 of the SmPC should reflect all available information on reproductive and developmental toxicity for both compounds.

Genotoxicity
No specific carcinogenicity study has been carried out with the aliskiren/valsartan combination. Aliskiren alone gave negative results in a battery of in vitro and in vivo tests.

Carcinogenicity studies
No specific carcinogenicity study has been carried out with the aliskiren/valsartan combination; likewise, no chronic (26 or 52wk) toxicity study in rats with the combination has been performed

Ecotoxicity/environmental risk assessment
The applicant submitted an Environmental Risk Assessment related to the use of aliskiren/valsartan fixed dose combination tablets (150/160 mg and 300/320 mg) in hypertension treatment with the commercial name of SPV100. The active substances have been assessed separately and both triggered a Phase II – Tier A (PEC 1.5 µL and 1.6 µL, respectively). Aliskiren shows low acute and chronic toxicity towards aquatic organisms; partitioning to soil and bioaccumulation are not expected; photodegradation is expected to be minimal. The value of log Koc < 4 in the adsorption/desorption study suggests a low to moderate sorption to soil and sludge. It 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. Results of Tier B risk assessment on sediment dwelling organisms suggests that no risk for the sediment compartment is expected. Valsartan shows moderate chronic toxicity to aquatic species. The most sensitive endpoint is the reproduction rate in *Daphnia magna*. It is not readily biodegradable and it is not expected to bioaccumulate. Adsorption to sludge has been found to be low. The study on the transformation of valsartan in aerobic water-sediment systems revealed some partitioning of valsartan into sediment.

The environmental risk assessment, dated 18 March 2010, has been updated by the applicant to reflect the information provided in the responses to some questions raised in the first wave, which can generally be considered satisfactory. It's to be noted that the data presented for valsartan in the questions raised at D120 (45, 46, 47-B and 48-A) have already been discussed and endorsed by the CHMP during the procedures for the Diovan new paediatric indication (as type II variation (EMA/H/A-29-PAD/1219) for the film-coated tablet and new marketing application authorization for the liquid formulation (EMA/H/A-29-PAD/1220)) and the Exforge HCT marketing application authorization (CP/H/C/001068). A follow-up measure resulting from the Exforge HCT approval was filed mid-June 2010.

Discussion on non-clinical aspects

No specific studies with the SPV100 fixed combination have been 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 the Applicant referred to previous studies conducted with the single components aliskiren and valsartan, 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. Most of the studies included in the dossier were carried out in healthy volunteers, and therefore were clinical in nature. Animal toxicokinetic –but not pharmacokinetic- data have been obtained from sub-groups of animals within the pivotal 2-week and 13-week repeated dose toxicity studies. Further support for limiting the number of specific studies in the non-clinical development plan derived from the indications of the EMEA/CHMP/SWP/258498/2005 guideline in order to reduce the use of experimental animals. Overall, the non-clinical developmental plan was limited to a minimum essential number of studies. This can be accepted, considering that a substitution indication is requested, and that the plan has been discussed with several EU national Agencies before implementation.

Only two non-clinical toxicity studies were performed using free combination of ALI and VAL to support the present application, reported as n. 0510044 and n. 0680120. Study n. 0510044: "2-week oral dose range finding study in rats in combination with Valsartan" was conducted in-house by Novartis according to GLP-like high standards of scientific quality. The 13-week GLP study (Report No. 0680120): "A 13-week oral gavage toxicity study in the rat followed by a 4 week recovery" was performed in the period September-December 2006 at the Charles River Laboratories Preclinical Service Montreal. The study was conducted and reported in compliance with the current requirements of the GLP regulations. However, further evidence of GLP compliance and of appropriate inspection/auditing had been required concerning the conduct of studies 802359, Novartis ref: 0680120 and 802895, Novartis ref: 0770449.
The applicant has provided supporting documents that give the necessary assurance that the pivotal 13-week toxicity study in rats (Study 802359) and the 4-week study to qualify impurities (Study 802895) have been conducted and reported in full compliance with GLP requirements.
Overall, these studies raised no major concerns on the potential toxicity of SPV100 association; GI toxicity observed at the higher dose level with aliskiren/valsartan could be attributed to the valsartan component and tended to be reversible. GI lesions did not appear to be associated with changes in absorption of both aliskiren and valsartan.

The only major finding of the sub-chronic 13-week study was a marked interaction of valsartan on circulating levels of aliskiren (AUC_{0-24h}), which were reduced by about 80% compared to aliskiren given alone; the effect was observed at the dose level 300/300 mg/kg. This finding was consistent with the 26% decrease observed in healthy volunteers treated with aliskiren 300 mg alone or aliskiren plus valsartan 320 mg. Such interaction did not appear to be related to interference with the CYP pathways or with MRP1 or -2 transporter systems; the possible action mechanism remained to be clarified, nor was the issue discussed in the Non-Clinical Overview. The 26% decrease observed in humans following therapeutic dosages of the drugs was claimed to be clinically irrelevant, with no further explaination or discussion. A point of clarification was therefore raised in the D120 LoQ - Clinical (PK) part. Please refer to the relevant assessment for the discussion of this issue.

The applicant had been asked to discuss whether the impurities 001-04, 002-04 and 503-03 have already been identified and qualified in the aliskiren dossier, or whether they have arisen as a consequence of the new formulation. New impurities identified should be qualified in relation to their genotoxic potential.
The applicant has provided an adequate response to this issue, clarifying that 001-04 and 002-04 were adequately qualified at the proposed specifications for SPV100 by two in vitro genotoxicity assays and a 4-week rat toxicity study performed with aliskiren drug substance spiked with each of these impurities. The drug substance impurity 503-03 is structurally identical to a metabolite of aliskiren in the main toxicology species and in humans and is therefore considered to be qualified by the extensive non-clinical toxicology programme that is available for aliskiren. The impurity was also present in sufficient amounts in aliskiren drug substance used during two in vitro genotoxicity assays and a 13-week toxicity study in rats to further support qualification of 503-03 at the proposed specification.

The Environmental Risk Assessment submitted, including the responses to the questions raised in the first wave, is considered adequate.

Conclusion on non-clinical aspects
All concerns on the non-clinical part of the dossier have been solved with the exception of the marked interaction of valsartan on circulating levels of aliskiren (AUC_{0-24h}), which were reduced by about 80% compared to aliskiren given alone; the effect was observed at the dose level 300/300 mg/kg. This finding is consistent with the 26% decrease observed in healthy volunteers treated with aliskiren 300 mg alone or aliskiren plus valsartan 320 mg. This issue is addressed in the clinical part of the dossier.

III.3 Clinical aspects

- **Tabular overview of clinical studies**

Summary of biopharmaceutic studies

Study	Objective	Population		Dosage form	Dose	N
CSPV100A2104	Pilot relative bioavailability	HS	M/F	Aliskiren (FMI) Valsartan (CSF)* Aliskiren/Valsartan (TIC, MG1)	150 mg SD 160 mg SD 150/160 mg SD	36
CSPV100A2111	Definitive Bioequivalence	HS	M/F	Aliskiren (FMI) Valsartan (CSF)* Aliskiren/Valsartan tablet (FMI)	300 mg SD 320 mg SD 300/320 mg SD	84
CSPV100A2114	Food-Effect	HS	M/F	Aliskiren/Valsartan tablet (FMI)	300/320 mg SD	34

HS = Healthy subjects, M = Male, F = Female, SD = Single dose, FMI = Final market image, CSF = Clinical service form, TIC = fixed combination capsule (tablet-in-capsule), MG1 = film-coated bilayer tablet (melt granulation variant 1), *Valsartan CSFs were identical to the EU approved formulations with the minor exception of the colour of capsule shell.

Reference: [Synopses of individual studies] [Tabular listing of all clinical studies]

No new pharmacodynamic (PD) study has been submitted. A study investigating the PD of the combined administration of aliskiren and valsartan was submitted with the Rasilez dossier (Study No. **CSPP100A2101**). A pharmacokinetic drug-drug interaction study between aliskiren and valsartan (**CSPP100A2216**) is submitted in support of this submission. This study was also reviewed as part of Rasilez monotherapy.

Overview of Efficacy/Safety Studies

Topic	Source of data
Dose selection studies	None
Patients with essential hypertension	
Pivotal efficacy and safety study Short-term (8 weeks) placebo-controlled efficacy and safety study	**Study CSPP100A2327:** Phase III**,** randomized, double-blind, 4-arm factorial, parallel group, multi-center, placebo controlled dose escalation study; pivotal study.
Pivotal long-term safety study (12 months)	**Study CSPV100A2301*:** Phase III, 54 week, open-label, multicenter study to assess the long term safety and tolerability of the combination of aliskiren 300 mg/valsartan 320 mg.
Supportive study Short-term (8 weeks) placebo-controlled efficacy and safety study	**Study CSPP100A2203:** Phase II, randomized, double blind, multifactorial, placebo controlled, parallel group. Designed as a pivotal trial for efficacy and safety of aliskiren monotherapy, and as proof-of-concept trial for the aliskiren/valsartan combination; supportive study.
Patients with essential hypertension not adequately responding to HCTZ 25 mg monotherapy	
Supportive study Short-term (8 weeks) active-controlled efficacy and safety study	**Study CSPP100A2331, supportive study:** Phase III, double-blind, active-controlled study evaluating the combination of aliskiren/valsartan/HCTZ (300/320/25 mg), aliskiren/HCTZ (300/25 mg), valsartan/HCTZ (320/25 mg), and HCTZ 25 mg.

*In this study, open-label addition of HCTZ was permitted in patients whose BP was not adequately controlled by treatment.

Pharmacokinetics

Pharmacokinetics of aliskiren and valsartan have been reviewed and assessed in previous submissions (Rasilez®, Diovan® and Rasilez HCT®).

Aliskiren. Aliskiren shows a very low bioavailability (2.6%). Absorption is probably also mediated by unidentified active transporters. Food markedly decreases aliskiren bioavailability by about 70%. Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration. Aliskiren is poorly metabolised and is excreted mainly as unchanged drug into the bile, its urinary excretion being minimal. Hepatic uptake and biliary excretion are predominantly mediated by transporters. Plasma clearance was found to be 0.13 L/h/kg. Terminal half-life is about 40 h (ranging from 30 to 60 hours) and was found to be slightly longer in the elderly (>65 years). In the elderly (>65 years), exposure is increased by about 50%, with respect to subjects aged 18-45 years. In subjects with renal impairment Cmax and Cmin are both about 2-fold higher than in subjects with normal renal function. The increase appear to be not related to the decrease of renal function. In subjects with hepatic impairment, exposure is not increased. Time needed to reach steady-state is 7-12 days. The accumulation factor is 1.5-2. Apparent clearance did not change with repeated administration. Pharmacokinetics slightly deviated from linearity in the whole range of investigated doses. Pharmacokinetics of aliskiren were found to be highly variable. The inter-subject variability for Cmax and AUC was 40-70% and 30-50%, respectively. The intra-subject variability for aliskiren Cmax and AUC was 40% and 20%, respectively. Aliskiren does not inhibit any of the CYP450 enzymes at therapeutic concentrations. *In vivo* data suggest that aliskiren is not an enzyme inducer. When administered with atorvastatin, steady-state aliskiren AUC and C_{max} increased by 50%. An interaction study with ciclosporin has shown that ciclosporin increased aliskiren AUC by 4.5 to 5.5-fold, and Cmax by 2.5-fold, independently of ciclosporin dose. Ciclosporin markedly increased aliskiren $t_{1/2}$. This result confirms that P-gp is a major determinant of aliskiren clearance.

Valsartan. Following oral administration, the peak plasma concentrations of valsartan are reached in 2 to 4 hours. Absolute bioavailability is about 23%. The absorption of valsartan shows high variability. Typically, coefficients of variation for the plasma valsartan AUC are in the range of 30-50% after an

oral dose. The mean systemic availability of valsartan (capsules) is reduced when given with a high fat meal (59% and 48% decrease in Cmax and AUC, respectively). The impact on the pharmacodynamic response is not considered clinically relevant, and therefore valsartan may be administered with or without food. The total plasma clearance (2.2 L/h, 2% of hepatic blood flow) and volume of distribution at steady-state (16.9 L, 0.4X total body water) indicates that valsartan has low liver extraction and it does not distribute into tissues extensively. Circulating valsartan is about 94-97% bound to serum proteins, mainly serum albumin. Valsartan undergoes little metabolic conversion. Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. Mean oral half-life is approximately 6 hours.
The exposure of valsartan (AUC and Cmax) is linear/dose proportional in the dose range 80-320 mg. There is no change in the pharmacokinetics of valsartan on repeated daily administration, and accumulation is minimal when dosed once-daily. Exposure (measured by AUC0-∞) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. This is not thought to be of clinical relevance when data from the elderly patient population are considered. Therefore, no dosage adjustment is necessary. There is no apparent correlation between renal function and exposure to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients. As the majority of valsartan is excreted in the bile, biliary restriction is expected to increase systemic exposure. Mean exposure (AUC) to valsartan was increased 2- fold in patients with mild and moderate impairment of liver function. Given the observed increase in exposure and the wide therapeutic index for valsartan, no dose adjustment is considered necessary in patients with mild to moderate impairment of liver function. It is contraindicated in patients with severe liver disease, biliary cirrhosis and cholestasis. No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with warfarin, amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin.
A drug-drug interaction study (study number SPP100A2216) was submitted with the Rasilez® dossier. This study was an open label, multiple dose study to evaluate the pharmacokinetic drug-drug interaction at steady-state between valsartan (320 mg) and aliskiren (300 mg) when given alone or in combination to healthy volunteers. The study showed that co-administration with valsartan lowers the AUC for aliskiren by 26%, but left substantially unchanged valsartan PK parameters. The applicant claims that the interaction between aliskiren and valsartan are "not clinically relevant" but no justification is given to support this claim. The mechanisms responsible for the decreasing effect of valsartan on aliskiren bioavailability are unknown, but it seems likely that the interaction occurs during the absorption phase. Because the DDI was performed under fasting conditions, it is not known whether the findings of the study can also be extended to fed conditions, i.e., those recommended by the SmPC. The decrease in aliskiren bioavailability caused by valsartan may be additive with the decrease caused by food and this may have an influence on the blood pressure decreasing effect of the combination.
The proposed SmPC should contain information on the interaction between the components when administered under fed conditions, as recommended by the SmPC.

Bioequivalence. The core studies for the registration of Rasival were conducted with the free combination of aliskiren and valsartan (300 mg aliskiren film-coated tablet and 2x160 mg valsartan capsule). Therefore, the Applicant conducted a bioequivalence (BE) development program to bridge the clinical efficacy and safety data obtained with aliskiren and valsartan in free combination to the fixed combination final market image (FMI) tablets. A definitive BE study was carried out for the higher 300/320 mg strength. The aliskiren reference formulation was the same as the EU approved formulation. The valsartan reference formulation was the same as the EU approved formulation with the only minor difference of the colour of the capsule shell. The difference in colour was required for blinding purposes in the pivotal efficacy and safety studies and is not considered to affect the pharmaceutical properties of the product. Drug products were administered under fasting conditions. The study employed an open-label, randomized, single dose, two period, two sequence, crossover design. Washout between treatments was 14 days. The subjects enrolled were both males and females healthy non-smoking volunteers. The study was correctly designed and carried out. Sample size was adequate. Washout between treatments allowed complete elimination of the drugs before the next treatment period. Number of blood sampling time-points was adequate to have AUC0-tlast values ≥

80% of AUC0-inf. The results of the study show that under fasting conditions, the fixed combination FMI tablets are bioequivalent to the free combination forms.

With regard to the **biowaiver request** for the 150/160 mg dose strength, the Applicant has provided data showing dose proportionality for valsartan. For aliskiren, the provided data showed deviation from true dose proportionality (a 2-fold increase in dose results in about a 2.5-fold increase in AUC and Cmax). The applicant justifies use of the highest dose of aliskiren as having the most ability to discriminate difference. The argument of the applicant is acceptable. The biowaiver request for the 150/160 strength is therefore considered acceptable, being supported by all the data and information required by the BE Guideline.

The influence of a high-fat meal on the bioavailability of the 300/320 mg aliskiren/valsartan fixed combination FMI tablet was investigated in an open-label, randomized, single dose, two period, two sequence, crossover study. Based on the geometric mean ratios, aliskiren AUC and Cmax under fed conditions were reduced by 76% and 88%, respectively, when compared to fasted conditions. Administration under fed conditions further increased the variability of aliskiren PK. The study confirms the very marked decrease in aliskiren bioavailability elicited by food. The decrease found in the present study was higher than that found in previous studies. In addition, the fed/fasted $AUC_{0\text{-tlast}}$ ratio was below 0.21 in 12 subjects out of 29. Thus, in about 40% of subjects food reduced the bioavailability of aliskiren by 80%. These observations suggest that the food effect may be larger with the aliskiren/valsartan FDC, possibly because the reducing effects of valsartan and food on aliskiren bioavailability are more than additive in this formulation. The CHMP's position is that the results raise concern that the food effects in the fixed and free combinations may be different. Therefore, a bioequivalence study comparing the free and fixed combination directly in the fed state is required to address this point.
recently completed study showed that aliskiren bioavailability was also reduced by a light meal. The Applicant proposes for Rasival the same posology recommendation "should be taken with a light meal" as Rasilez® (and Rasilez®-HCT). This will ensure a consistent treatment effect of aliskiren when the therapy is switched from the free combination to the fixed combination.

Pharmacodynamics
No new pharmacodynamic (PD) study has been submitted.
A study investigating the PD of the combined administration of aliskiren and valsartan was submitted with the Rasilez dossier (Study No. CSPP100A2101). In this study, the PD effects of single dose administration of aliskiren (150 and 300 mg) were compared to those of valsartan and aliskiren + valsartan in high and low sodium status. The purpose of the study was to investigate whether the combination of aliskiren and valsartan would produce additive effects under two conditions of sodium intake in normotensive healthy volunteers before performing a factorial design trial in hypertensive patients. The hypothesis tested in the study was that the combination of low-to-moderate doses of aliskiren and valsartan would inhibit the RAS and decrease BP more effectively than either blocker given alone at a higher dose. The primary PD parameter was RC (active renin); secondary PD parameters were plasma renin activity by trapping assay (PRA-TR), PRA-TR/active renin ratio (Ang I production rate), plasma pro-renin (difference between total renin and active renin), plasma aldosterone, plasma Ang I and Ang II, blood pressure, urinary sodium excretion, and free urinary aldosterone concentration. In the high sodium panel both drugs given alone or in combination markedly increased plasma active renin levels from baseline within 4 hours of drug intake. The increase after aliskiren 300 mg was similar to that after aliskiren 150 mg + valsartan 160 mg, both being greater than the increase after valsartan 320 mg. As expected, aliskiren and valsartan had opposite effect on PRA, Ang I and Ang II. In subjects treated with the combination, the inhibitory effect of aliskiren on PRA, Ang I and Ang II predominated, completely antagonising the valsartan-induced increase of these parameters. In comparison with placebo, aliskiren 300 mg, valsartan 320 mg and aliskiren 150 mg + valsartan 160 mg all decreased plasma aldosterone concentrations for 4 hours in a similar manner. In parallel, urinary aldosterone concentrations were lower after administration of aliskiren 300 mg, valsartan 320 mg and aliskiren 150 mg + valsartan 160 mg than after administration of placebo, with no difference in pattern among the active treatments for 4 hours post-dose. Compared to placebo, aliskiren 300 mg and aliskiren 150 mg + valsartan 160 mg suppressed urine aldosterone excretion for up to 24 hours after drug intake, whereas the effect of valsartan 320 mg on urinary aldosterone concentration persisted for no more than 18 hours. All active treatments decreased diastolic and systolic blood pressures, the peak effect being at around 6-9 hours post-dose and returning to baseline values by 36-48 hours post-dose. No difference was apparent among the active

treatments. A reflex increase in pulse in response to the drop in blood pressure was also observed. In the low panel group, essentially similar results to those of the high sodium panel were found for all PD parameters, including blood pressure.
The claim that addition of a direct renin inhibitor (aliskiren) to an angiotensin receptor blocker (valsartan) may result in a more effective lowering of blood pressure is a supposition and has not yet been demonstrated: the claim is the basis for study reports submitted in the current application.

Discussion on clinical pharmacology

The main objection that has been raised by CHMP on clinical pharmacology pertains to the follow issue:

1) *A) The bioequivalence of the fixed combination to the free combination has not been shown in the fed state. It is considered that a bioequivalence study in the fed state as described in the proposed SmPC is required and the applicant should provide the results of such study.*
   B) In addition, the Applicant should provide PK and PD data of a study investigating the effects of a light meal vs. fasting conditions with the two strength doses (150/160mg and 300/320mg).

Additional issues are:

2) *Co-administration with valsartan lowers the AUC for aliskiren by 26%. The claim by the applicant that the interaction between aliskiren and valsartan are "not clinically relevant" requires adequate justification.*

3) *The food effect study shows that after aliskiren/valsartan combination, the aliskiren AUC reduction by high fat meal was even higher than that found in previous food-effect studies with aliskiren alone. Therefore, it is possible that the decreasing effect of valsartan and food on aliskiren bioavailability is more than additive. The Applicant is asked to address this point.*

4) *The recently completed study investigating the effect of the light meal on PK parameters of aliskiren show that light meal significantly reduces aliskiren Cmax and AUC to a similar extent as a high fat meal. Therefore, the Applicant is asked to provide data to show the effects of a light meal on PK and PD parameters after administration of the FDC aliskiren/valsartan combination.*

1) *A) The bioequivalence of the fixed combination to the free combination has not been shown in the fed state. It is considered that a bioequivalence study in the fed state as described in the proposed SmPC is required and the applicant should provide the results of such study.*
   B) In addition, the Applicant should provide PK and PD data of a study investigating the effects of a light meal vs. fasting conditions with the two strength doses (150/160mg and 300/320mg).

A) As stated in the EMA guidance (CPMP/QWP/EWP/1401/98 Rev 1, January 2010), bioequivalence studies conducted under fasted condition are more sensitive and therefore represent of the "worst case" to test bioequivalence.
However, the same guideline states: "*For products where the SmPC recommends intake of the reference medicinal product only in fed state, the bioequivalence study should generally be conducted under fed conditions.*" The SmPC for aliskiren monotherapy (and hence for this combination product) states that the product should be taken in the fed state: a bioequivalence study in the fed state is therefore expected.

Nonetheless, it is acknowledged that EMA guidance states that studies should "generally be conducted in the fed state" where the SmPC states that the product should be taken in the fed state i.e. the guidance is not definite but allows room for manoeuvre.

Food intake does not affect valsartan pharmacodynamics and therefore, the valsartan SmPC states that it can be taken without regard to meals.

The bioavailability of Aliskiren is reduced by food. The Applicant provided in-house study data in support of his claim that the effect of food on aliskiren bioavailability is intrinsic to its physicochemical properties and is independent of the formulation, meal content, dose timing and the drug with which it is being combined. On these bases, the Applicant considers that fasted conditions are appropriate to investigate the bioequivalence of the proposed formulation of aliskiren/valsartan fixed combination. A BE study in the fed state is not expected to provide additional valuable information in addition to existing data.

It is however considered that the in-house study data presented by the applicant do not provide a convincing rationale to waive this requirement for a bioequivalence study in the fed state. The following table 54-1 shows that the largest food effect seen in all the studies conducted was for the combination intended for licensing, where a 76% decline is aliskiren AUC was seen. This is certainly larger than what was seen for the early development formulation (63%): it is noted that the confidence intervals for the changes do not overlap. While such cross-trial comparisons are not conclusive, there is concern that (i) some aliskiren formulations may have a larger food effect than others and that (ii) formulations containing aliskiren that are bioequivalent in the fasted state may not be bioequivalent in the fed state. This is considered to be an important issue because it is proposed to administer the fixed combination in the fed state: a bioequivalence study in the fed state is required to address concerns. Patients currently taking the free combination should expect to receive the same exposure if switched to this fixed combination.

Table 54-1 Comparison of food effect studies with aliskiren

Program	Study	Meal	Formulation	Dose (mg)	% AUC Δ	90% CI
Monotherapy	CSPP100A0026	High fat	FCT	150	62%↓	53% - 69%
Monotherapy	CSPP100A2207	High fat	FCT	300	71%↓	66% - 76%
Monotherapy	CSPP100A2113	Low fat	FCT	300	68%↓	61% - 73%
Monotherapy	CSPP100A2110*	Low fat	FCT	300	67%↓	59% - 73%
Aliskiren/HCTZ FDC	CSPH100A2104	High fat	FCT	300/25	60%↓	54% - 66%
Aliskiren/Valsartan FDC	CSPV100A2103	High fat	FCT**	150/160	63%↓	55% - 69%
Aliskiren/Valsartan FDC	CSPV100A2114	High fat	FCT	300/320	76%↓	72% - 79%

FDC = fixed dose combination, FCT = film-coated tablet, **early development formulation

*Food effect was evaluated at steady state (AUC_{τ} and $C_{max,ss}$)

The applicant has also provided published data in support of a claim that fasted studies may be extrapolated to the fed state: the applicant refers to studies on abacavir and nicardipine and nadolol tablets in fed and fasted states and claims that the conclusions of these studies are applicable to the current product. This argument is considered to be weak since it relies on individual studies (that may or may not be applicable to the current product) rather than a published review/critique of interpretation.

The conclusion drawn by the applicant that study SPP2110 demonstrates that fed (light meal) and fasting conditions have a similar impact on aliskiren effect on PRA and BP is not shared. As acknowledged by the Applicant the study was not powered to detect differences between groups in blood pressure, thus the only PD parameter that was shown no to be effected by food intake is PRA. Therefore results from the food effect study SPP2110 do not remove the need for a fed bioequivalence trial. It is also noted that the applicant has provided PD data for aliskiren monotherapy only and not for the fixed combination in question: the fixed combination may have a larger food effect.

B) The Applicant has not directly addressed this point. However, because the additional issues 2-4 are all related to the same concern, the response can be extrapolated from the response to the issues 2-4, and the conclusion can be drawn after assessing these responses.

2) *Co-administration with valsartan lowers the AUC for aliskiren by 26%. The claim by the applicant that the interaction between aliskiren and valsartan are "not clinically relevant" requires adequate justification.*

3) *The food effect study shows that after aliskiren/valsartan combination, the aliskiren AUC reduction by high fat meal was even higher than that found in previous food-effect studies with aliskiren alone. Therefore, it is possible that the decreasing effect of valsartan and food on aliskiren bioavailability is more than additive. The Applicant is asked to address this point.*

4) *The recently completed study investigating the effect of the light meal on PK parameters of aliskiren show that light meal significantly reduces aliskiren Cmax and AUC to a similar extent as a high fat meal. Therefore, the Applicant is asked to provide data to show the effects of a light meal on PK and PD parameters after administration of the FDC aliskiren/valsartan combination.*

In reference to **point 2**), it is acknowledged that, on the basis of the pharmacodynamic results of the DDI study, it can be concluded that the change in aliskiren AUC should not affect the contribution of aliskiren to the reduction in blood pressure. In fact, co-administration of aliskiren/valsartan prevented the reactive rise in PRA observed with valsartan alone; the aliskiren/valsartan combination reduced plasma aldosterone levels at 24 hours; and both systolic and diastolic pressure were lower during combination treatment compared to monotherapy with aliskiren or valsartan. In addition, aliskiren displays high-variability and the AUC reduction was less than this variability.
However, because the DDI was performed under fasting conditions, and the interaction between the two drugs apparently occurs at the absorption site, it is not known whether this conclusion may also be extended to fed conditions, i.e., those recommended by the SmPC. The decrease in aliskiren bioavailability caused by valsartan may be additive with the decrease caused by food and this may have an influence on the blood pressure decreasing effect of the combination because under these conditions aliskiren may not reach effective levels, particularly with the 150/160 mg dose strength. The Clinical Overview accompanying the food effect study CSPP100A2110 reports the results of a PK-PD analysis, and states that, for aliskiren *"There appeared to be a threshold plasma concentration that is required to impact PRA. The minimum plasma concentration to give maximal PRA inhibition (0.1 ng/mL/hr) was ~15 ng/mL".* Data from Study SPP1000026 of the Rasilez submission dossier showed that after a single administration of aliskiren 150 mg, mean Cmax was 12.6 ng/mL. Thus, after a single administration of aliskiren 150 mg, Cmax was lower than the minimum plasma concentration needed to give maximal PRA inhibition. Obviously, Cmax is expected to be higher at steady-state (accumulation factor is about 1.5), but it must be considered that valsartan reduced aliskiren Cmax,ss by 28%. Thus, it is possible that when the 150/160 mg FDC dose strength is administered with food, aliskiren does not reach a therapeutic level.
The CHMP suggests that the proposed claim ("the 26% reduction in aliskiren AUC by concomitant valsartan administration does not affect the reduction in blood pressure produced by aliskiren") should not be included in the SmPC until it is verified that the reduction in aliskiren AUC does not affect the aliskiren contribution to the blood pressure decrease, also under fed conditions.

In reference to **point 3**), the Applicant claims that because reduction in steady state aliskiren AUCτ by valsartan was 26%, and reduction in aliskiren AUCinf after administration of 300/320 mg aliskiren/valsartan fixed-dose combination with food was 76%, the separate food/interaction effects were not additive (71%+26% = 97%). In addition, the Applicant notes that the comparison of the 90% CIs for the AUC change in all food effect studies indicates a degree of variability and an overlap, suggesting that the overall AUC decrease in study CSPV100A2114 (aliskiren/valsartan) is similar to that observed in previous studies.
However, the FDC food effect studies compared BA of aliskiren in fasting *vs.* fed conditions, both in presence of valsartan. Thus, these studies cannot be used to evaluate the additive effect of food + valsartan, which should be evaluated by comparing AUC of aliskiren/valsartan (fed) *vs.* AUC of aliskiren alone (fasting). The combined effect of valsartan and food may have an impact on the aliskiren contribution to the BP lowering effect of the combination administered with food, particularly

with lowest strength dose (150/160 mg). The Applicant should provide the data of the food effect study performed with the 150/160 mg dose strength, which was not submitted with the original Dossier.

In reference to **point 4**) the Applicant claims that he PK/PD results presented for the monotherapies are considered to be applicable to, and relevant for, the aliskiren/valsartan combination since aliskiren food effect is intrinsic to its physicochemical properties and is independent of the formulation, meal content (low fat or high fat) and the drug with which it is being combined. Therefore, the PK/PD data for aliskiren/valsartan fixed-dose combination can be extrapolated based on the known pharmacodynamic properties of aliskiren (CSPP100A2110), valsartan (SmPC) and the aliskiren/valsartan combination (CSPP100A2327).
However, it is considered that there are no data supporting the claim that the PK/PD data of the aliskiren 'light meal' study (CSPP100A2110) can be extrapolated to the FDC. Co-administration with valsartan can further reduce aliskiren absorption, when administered with food. Under these conditions, aliskiren may not reach effective levels, particularly with the 150/160 mg dose strength.

In conclusion, the Applicant has not satisfactorily addressed the concern expressed in the point b) of the Major Objection.

Conclusions on clinical pharmacology

Demonstration of BE under fasting conditions cannot be extrapolated to fed conditions, because the aliskiren food effect may also depend on formulation. Therefore, formulations containing aliskiren that are bioequivalent in the fasted state may not be bioequivalent in the fed state. This is considered to be an important issue because it is proposed to administer the fixed combination in the fed state: a bioequivalence study in the fed state is required to address concerns. Patients currently taking the free combination should expect to receive the same exposure if switched to this fixed combination. A BE study under fed conditions is therefore considered necessary, as required by the Major Objection.

It is still not known whether aliskiren can reach therapeutic levels when administered with food in combination with valsartan, taking into account that both food and valsartan decrease aliskiren bioavailability. This is particularly true for the lowest FDC dose strength, 150/160 mg. Available data suggest that when co-administered with food and valsartan, aliskiren levels may not reach the minimum plasma concentration needed to give optimal PRA inhibition. A study assessing the effect of fed and fasting conditions on PK and PD (PRA and Blood Pressure) of the FDC aliskiren-valsartan is therefore considered necessary.

Clinical efficacy

Dose-response studies and main clinical studies
Aliskiren and Valsartan are approved in the treatment of essential hypertension: aliskiren is an inhibitor of renin activity whilst Valsartan is an Angiotensin II receptor blocker (ARB). Treatment with valsartan increases renin secretion and renin activity. The combination of aliskiren and valsartan is expected to achieve an effective inhibition of the RAS.

The clinical program in this submission aims to prove the efficacy and the safety of the combination of aliskiren/valsartan in the treatment of essential hypertension with the limited indication of "substitution" treatment, that is a combination that the physician can prescribe in hypertensive patients who are already stably controlled by the two drugs.

For analyses on efficacy, the clinical program includes one main new study and two non-new supportive studies. For analyses on safety, the clinical program includes one new long-term main study.

Main study (study 2327). This was a double-blind, randomized, four-arm parallel-group, multicentre, placebo- and active- controlled, dose escalation study (4 week LDC followed by 4 week HDC). The methods are substantially in agreement with EMEA guidelines for parallel studies on hypertension including type of patients (adults with uncomplicated essential hypertension stage 1-2), duration (active treatment lasting 8 week preceded by wash-out and run-in on placebo),

outcomes/endpoints (blood pressure change, control of hypertension, and biomarkers), sample size, randomisation, blinding, monitoring (compliance, efficacy, and safety), and statistical methods.
The main methodological concern is that aliskiren was not administered under standardized conditions that were indicated by the CHMP (with a light meal) to reduce the variability of aliskiren's pharmacokinetics and pharmacodynamics due to the effects of fat meals on aliskiren absorption.
The study initiated in June 2005 and terminated on September 2006 and was conducted in 312 centers from US, Germany, and Spain. Compared to the two arms treated with each monocomponent (n completed = 384 for aliskiren and 412 for valsartan), the antihypertensive effect of the combination in the arm treated with the combination (n completed = 409) was significantly higher in analyses on msSBP, msDBP, control rate of hypertension and on 24-hour blood pressure in the subgroup with data ($P<0.001$). Findings were consistent at various time points and similar between LDC and HDC. Effects on biomarkers were consistent with previous data showing an increase in renin activity during treatment with valsartan but not during treatment with aliskiren.

Supportive study 2203. This was a double-blind, randomized, multi-arm parallel-group, multicentre, placebo- and active- controlled, study in adults with untreated hypertension stage 1-2. The primary objective was to analyze the effects of aliskiren given alone versus placebo administered for 8 weeks in patients with hypertension stage 1-2. **Thus, for this application, the study is of limited interest.**
The study included many secondary objectives but without adequate statistical power. The number of completed patients was ≤56 in each one of the three arms treated with the combination aliskiren+valsartan (75/80 mg, 150/160 mg and 300/320 mg), ≤55 in each one of the three arms treated with valsartan alone (80, 160, and 320 mg), and ≤166 in each one of the three arms treated with aliskiren alone (75, 150, and 300 mg). Compared to the monocomponents, the combination aliskiren+valsartan induced a blood pressure reduction that was always numerically superior but never significantly higher.
The CHMP concluded that the results of this study are in contrast with the results of the pivotal study 2327 and raise doubts about the efficacy of the FDC.

Supportive study 2331. This was a randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of the combination of aliskiren/valsartan/HCTZ (300/320/25 mg), compared to the combinations of aliskiren/HCTZ (300/25 mg) and valsartan/HCTZ (320/25 mg) administered for 8 weeks in patients with uncomplicated essential hypertension (stage 2, not stage 1) not controlled with HCTZ 25 mg. The antihypertensive effect of the combination aliskiren+valsartan+HCTZ was significantly higher than the effect of aliskiren+HCTZ or valsartan+HCTZ in all analyses ($P<0.05$). The study supports the evidence that the efficacy of the aliskiren+valsartan combination is higher than the efficacy of both monocomponents focusing on the limited subgroup of patients with stage 2 hypertension who are not controlled by HCTZ.
The results of this study are of limited interest to this application.

Discussion on clinical efficacy

The major concerns raised by CHMP on clinical efficacy are as follows:

1) The applicant has submitted the present application on the basis of a **wide therapeutic experience** of aliskiren and valsartan combination. Evidence in favour of a wide therapeutic experience has to be supplied

2) Study 2327 demonstrated that the combination product produced modest reduction in blood pressure compared to monotherapy whereas study 2203 failed to show a difference.

3) Study results are confounded by the fact that aliskiren was administered without a light meal as per CHMP indications.

4) Guideline CPMP/EWP/238/95 Rev. 2 indicates that studies for the evaluation of efficacy or safety are mainly performed in patients with mild to moderate hypertension, including patients of **both genders**, **elderly**, **patients with ethnic peculiarities** and concomitant illnesses such as **diabetes and renal disease, patients with severe hypertension**. Clarification of how the studies 2327 and 2301 comply with CPMP/EWP/238/95 Rev. 2 has to be supplied.

1) The applicant has submitted the present application on the basis of a **wide therapeutic experience** of aliskiren and valsartan combination.

CHMP/EWP/191583/2005 (Q&A on clinical development of fixed combination drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention) states:

> The substitution indication….approach is, in principle, only expected when tackling with drugs with a wide therapeutic experience and an adequately established benefit/risk ratio.

The wide therapeutic experience of the aliskiren valsartan combination has been questioned by the CHMP.
The applicant has not provided a convincing dataset to support the claim that aliskiren and valsartan have a wide therapeutic experience of use in combination.

The text of CPMP/EWP/238/95 Rev. 2 2004 (Guidance on clinical investigation of medicinal products for hypertension) reads as follows. " Usually a fixed combination serves as a substitute for a free combination provided that a normalization of blood pressure has been reached with the same doses of the individual components and the respective combination is well tolerated... it is mandatory that at least one pivotal clinical study is performed in a population of patients whose blood pressure cannot be normalized with monotherapy of one of the monocomponents, if this indication is claimed: ". The interpretation of the text is questionable. It could suggest that there is the need of add-on studies only if a claim is made about the use of the combination in patients whose blood pressure cannot be controlled with one of the monocomponents. This claim is not made by the applicant. The Applicant has not submitted results of pivotal add on studies.

The Applicant has been requested to provide:

A. the evidence in support of **a wide therapeutic experience** of aliskiren and valsartan at the doses proposed in the combination in the EU, possibly supported by data from other countries. In the absence of an adequate demonstration of wide therapeutic experience, the applicant is required to:
B. Justify the **pharmacological rationale of combining** these two substances and the **choice of dosages**.
C. Establish that **each active component** in the scheduled dosage **independently contributes towards efficacy.**
D. Establish an acceptable safety profile for the combined use of both substances in the relevant doses. Data from clinical trials and from the post marketing setting can be presented. Particular attention should be paid to patients at high risk for adverse events to inhibitors of the renin-angiotensin system (this point will be discussed in the safety section of this AR)

In response to point A, the Applicant has provided data showing that Aliskiren is presently approved in over 80 countries worldwide, and that a certain number of patients have used aliskiren as monotherapy or in combination with other anti-hypertensive drug(s), with aliskiren/valsartan in free or fixed combination, up to January 2010.

However, it is difficult to assess if the applicant adequately addressed the objection above because the EMA/CHMP guidelines do not indicate a precise definition of what is "a wide therapeutic experience". Nevertheless, although the current guidelines do not give definite guidance on the requirements for a claim of "wide therapeutic experience", the length of exposure to aliskiren valsartan combination is limited, being, at most, 28 months and inadequate to justify the claim of "wide therapeutic experience". It is the CHMP's opinion that a more appropriate market exposure would be at least 5 years (and preferably 10 years). Neither has the positive benefit-risk for each dose of the aliskiren-valsartan combination has been adequately established in the programme of clinical trials presented.

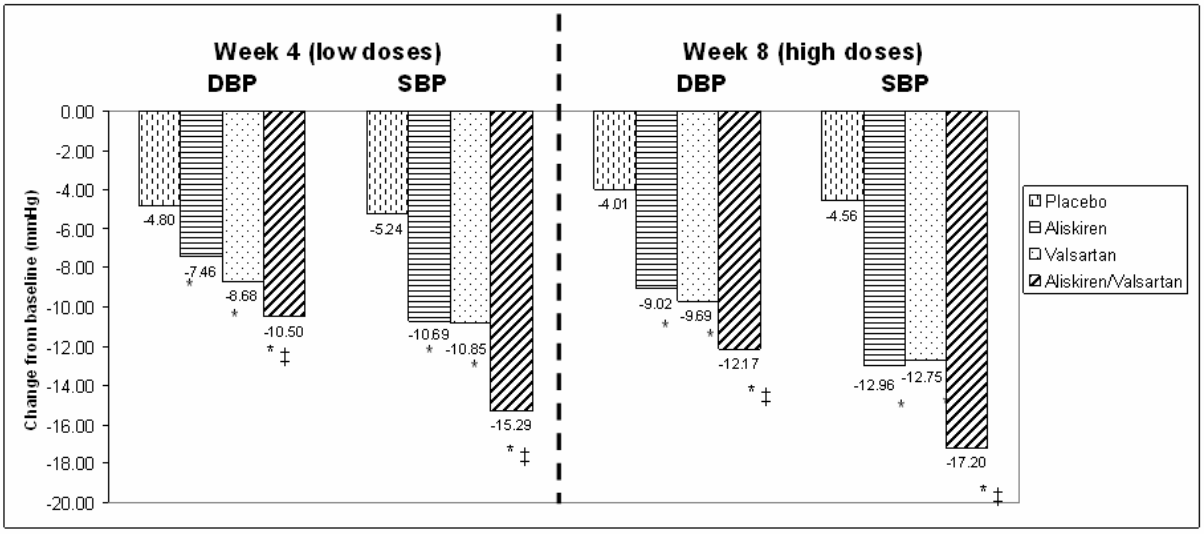
In response to point B, the applicant has provided: i) pharmacological-justification for the combination of the products as presented in the original submission, and ii) explanations on the choise of the dosage. The different and complimentary actions on the renin-angiotensin system of aliskiren

and ARBs are supposed to result in a complementary effect in providing optimal RAAS blockade. Available animal studies are consistent with the concept that renin inhibition, by aliskiren, can confer additional effective BP lowering when added to ARBs (Fossa, et al 1994; Wood, et al 2005). The concept that blocking renin activity may enhance the BP lowering response of other RAAS inhibitors is further supported by studies in which ACEi and renin inhibitors were combined. Additive BP responses were seen in rats when enalapril was combined with the renin inhibitor CP71362 (Mento, et al 1989). Synergistic BP responses were observed when captopril (Fossa, et al 1994) or benazepril (Wood, et al 2005) were combined with terlakiren and aliskiren, respectively.

Increase in plasma renin activity has been reported to be associated with increased risk of cardiovascular events. The potential organ protection of aliskiren in hypertensive patients has to be demonstrated. These general considerations on the potential additive effect on blood pressure of the fixed combination are acknowledged by the CHMP, as well as the Applicant's explanation that the choice of doses in the clinical program – low dose combination (LDC) = 150 mg aliskiren+160 mg valsartan; high dose combination (HDC) = 300 mg aliskiren + 320 mg valsartan -- were selected on the basis of previous studies and of the current marketed formulations of the two components, not on new dose-response studies.

In response to point C, the Applicant refers to study SPP2327 in support of the claim that each component contributes towards efficacy. Study SPP2327 was specifically designed to evaluate the efficacy and safety of aliskiren/valsartan combination and to assess whether each active monotherapy component contributed towards the efficacy of the combination. The study showed that each component of the combination independently contributes to the reduction of blood pressure and to the control of hypertension. (49.3% with the fixed combination vs 37.4% or lower with the monocomponents) (see table below).

The differences in blood pressure reduction and in hypertension control appear significant from statistical and medical viewpoints. Although the statistically significant parallel group study could fulfill the CHMP recommendations for a substitution indication, the small increment (reduction) in blood pressure on increasing dosage of the combination is considered as problematic (-15.29 *vs* -17.20).



*p<0.0001 vs placebo; ‡p<0.0001 vs each of aliskiren and valsartan except for aliskiren/valsartan 150/160 mg Vs. valsartan 160 mg where the p=0.0004.
Source: Clinical Study Report SPPA2327

Further concerns relate to the fact that the study did not establish a "plateau" blood pressure at 4 weeks to give reassurance that any blood pressure lowering effect beyond 4 weeks was not a function of an on-going effect of the lower dose. The applicant is requested to give reassurance that the blood pressure achieved at 8 weeks in study 2327 was significantly lower than that achieved at 4 weeks with the combination.

2) Study 2327 demonstrated that the combination product produced modest reduction in blood pressure compared to monotherapy whereas study 2203 failed to show a difference.

The BP lowering effect of the FDC (aliskiren/valsartan) seems to be not consistent throughout all the clinical studies. In fact, whereas in the pivotal short term (A2327) and long term (V2301) clinical studies the antihypertensive clinical efficacy was well documented, in supportive study (A2203) although the efficacy of the combination was numerically superior than that of monocomponents, the difference was not statistically significant.

The lack of statistical significance in study 2203 could depend on two factors: statistical power or absence of a true difference. The number of patients per arm in study 2327 is approximately 7-times higher than in study 2203. Thus, the results of study 2203 are not statistically significant because the study has a much lower statistical power as compared to study 2327.

3) Study results are confounded by the fact that aliskiren was administered without a light meal as per CHMP indications.

The clinical development program for the aliskiren/valsartan combination was conducted without regard to meals and data were not collected to assess the timing of drug administration in relation to food.
The CHMP questions how the clinical program was conducted in European patients disregarding the CHMP indication about the drug administration. Study SPP2110 did not adequately standardize the quality and the quantity of the light meal and leaves unsolved this important methodological point. There are no data supporting the claim that the PK/PD data of the aliskiren 'light meal' study can be extrapolated to the FDC. Co-administration with valsartan can further reduce aliskiren absorption, when administered with food (See PK section of this AR). Under these conditions, aliskiren may not reach effective levels, particularly with the 150/160 mg dose strength. It is the CHMP's opinion that a study to assess the effect of fed and fasting conditions on PK/PD (measurements of PRA and Blood Pressure) of Rasival is required. Applicant should also provide the food effect study and discuss the results with regards to the contribution of aliskiren to the BP lowering effect, taking into account the results of the analysis of the PK-PD relationship reported in the Clinical Overview accompanying the food effect study CSPP100A2110.

4) Guideline CPMP/EWP/238/95 Rev. 2 indicates that studies for the evaluation of efficacy or safety.... including patients of *both genders, elderly patients, patients with ethnic peculiarities* **and concomitant illnesses such** as *diabetes and renal disease, patients with severe hypertension.* **Clarification on how the studies 2327 and 2301 comply with CPMP/EWP/238/95 Rev. 2 has to be supplied.**

The clinical development program for Rasival did allow enrollment of :

i) elderly patients,

ii) patients with diabetes or moderate renal impairment (eGFR < 60 ml/min/1.73 m^2 - 44 diabetics and 11 subjects with moderate renal failure, received combination treatment)

iii) patients with heart failure and patients with stage 2 hypertension.

Regarding **severe hypertension**: 1044 subjects in study 2327 displayed bp > 160/100 mmHg. The applicant reports that (about) 38% of this group achieved "bp control". The CHMP acknowledges that these numbers are sufficient to comply with current guidelines.

The number of subjects with **diabetes and impaired renal function** with eGFR <60mL/min/SA is considered to be small: the applicant is requested to expand on:
i) if observational studies will add meaningfully to knowledge in these groups; or
ii) how the applicant intends to expand information in these groups.

The Applicant claims that the available data from the development program in patients **over 65 years of age, and according to gender** do support the conclusion that safety of aliskiren/valsartan in these subgroups is similar to effects observed in the overall population.

With regard to the claim for **age** groups, it is the CHMP's opinion that the applicant may not make claims for ages unless / until these issues have been adequately addressed and resolved.

With regard to the issue of **gender**, the VALUE study has shown a gender difference in the effect of valsartan with lack of significant benefit in women. This is of particular concern for this combination given the fact that MAH has reported no effect of aliskiren on ovarian renin activity that is a relevant source of renin in women and that differ from renin produced by the kidney.
The Applicant should investigate the possibility of a gender difference in the effect of Rasival on blood pressure
The Applicant acknowledges that the number of patients in **racial groups** other than Caucasian is too low to allow the general conclusion that results are applicable to all races.

Conclusions on clinical efficacy
Data indicate that the antihypertensive efficacy of the combination is higher than the efficacy of both mono-components in uncomplicated hypertension stage 1-2 (non-severe).
Lack of significant differences in secondary objectives of supportive study 2203 merely reflects the low statistical power of that study as shown by the fact that the number of completed patients in the specific arms of study 2203 is approximately 7-time lower than the n of completed patients in the main clinical study 2327.

Study SPP2327 showed that each component of the combination independently contributes to the reduction of blood pressure and to the control of hypertension. (49.3% with the fixed combination vs 37.4% or lower with the mono-components).

The differences in blood pressure reduction and in hypertension control appear significant from statistical and medical viewpoints. Although the statistically significant parallel group study could fulfil the CHMP recommendations for a substitution indication, the small increment (reduction) in blood pressure on increasing dosage of the combination is considered as problematic (-15.29 *vs* -17.20). Further concerns relate to the fact that the study did not establish a "plateau" blood pressure at 4 weeks to give reassurance that any blood pressure lowering effect beyond 4 weeks was not a function of an on-going effect of the lower dose.

There are no data supporting the claim that the PK/PD data of the aliskiren 'light meal' study can be extrapolated to the FDC. Co-administration with valsartan can further reduce aliskiren absorption, when administered with food. Under these conditions, aliskiren may not reach effective levels, particularly with the 150/160 mg dose strength. A study to assess the effect of fed and fasting conditions on PK/PD (measurements of PRA and Blood Pressure) of Rasival is required.

In reference to compliance to Guideline CPMP/EWP/238/95 Rev. 2: "…. including patients of **both genders**, **elderly patients**, **patients with ethnic peculiarities** and concomitant illnesses such as **diabetes and renal disease, patients with severe hypertension"**
The number of subjects with diabetes and impaired renal function with eGFR <60mL/min/SA is considered to be small and expanded information is required.
With regard to the elderly population, it is the CHMP's opinion that the applicant may not make claims for ages unless / until the issues raised have been adequately addressed and resolved.
With regard to issues of gender, the VALUE study has clearly shown a gender difference in the effect of valsartan with lack of significant benefit in women. This is of particular concern for this combination given the fact that MAH has reported no effect of aliskiren on ovarian renin activity that is a relevant source of renin in women, and that differ from renin produced by the kidney.

Clinical safety

The M.A.A. included safety data from 3520-treated patients, with 1225 patients exposed to the aliskiren/valsartan combination in short-term controlled clinical studies SPP2203, SPP2327, long-term

uncontrolled study SPV2301 and in an 8-week study SPP2331 where patients received the aliskiren/valsartan combination in addition to HCTZ.

The safety of aliskiren/valsartan was evaluated with an emphasis on the effects observed with the maximum recommended dose (300/320 mg) since if a good safety profile is established for the maximum dose, then safety of the lower dose can be assured.

The short term controlled studies have demonstrated that the incidence of total AEs, individual AEs, and discontinuation due to AEs in aliskiren/valsartan combination-treated patients were similar to those in monotherapy or placebo treated-patients (see Table 50-4).

Table 50-4 Number (%) of patients with most frequent AEs (>= 2% for any group) (safety population) by preferred term, Group A: short term, double-blind, placebo controlled studies

	Placebo	**Aliskiren**		**Valsartan**		**Aliskiren/Valsartan**	
Preferred term		**150mg N=615 n (%)**	**300mg N=569 n (%)**	**160mg N=514 n (%)**	**320mg N=487 n (%)**	**150/ 160mg N=506 n (%)**	**300/ 320mg N=473 n (%)**
Any adverse experience	225 (35.4)	164 (26.7)	121 (21.3)	143 (27.8)	102 (20.9)	124 (24.5)	93 (19.7)
Headache	56 (8.8)	21 (3.4)	10 (1.8)	20 (3.9)	13 (2.7)	15 (3.0)	11 (2.3)
Fatigue	9 (1.4)	6 (1.0)	6 (1.1)	11 (2.1)	3 (0.6)	10 (2.0)	6 (1.3)
Naso-pharyngitis	14 (2.2)	10 (1.6)	7 (1.2)	16 (3.1)	5 (1.0)	8 (1.6)	6 (1.3)
Back pain	11 (1.7)	7 (1.1)	7 (1.2)	3 (0.6)	7 (1.4)	5 (1.0)	3 (0.6)
Dizziness	11 (1.7)	8 (1.3)	7 (1.2)	6 (1.2)	7 (1.4)	5 (1.0)	4 (0.8)
Nausea	12 (1.9)	4 (0.7)	4 (0.7)	7 (1.4)	3 (0.6)	8 (1.6)	2 (0.4)
Bronchitis	6 (0.9)	3 (0.5)	4 (0.7)	1 (0.2)	5 (1.0)	0	5 (1.1)
Dyspnea	2 (0.3)	1 (0.2)	2 (0.4)	1 (0.2)	1 (0.2)	0	3 (0.6)

Source: [SCS-PT-Table 4.1-3]

Incidence of hyperkalemia (serum K >5.5 mmol/L) was higher with aliskiren/valsartan treatment (3.4%) than with monotherapy (aliskiren 1.2%, valsartan 1.0%) or placebo (2.1%) in short term studies (SPV SCS Table 3-3). The long term SPV2301 study (12 months) did not show an increased hyperkalemia compared to the short term studies (SPP2327 and SPP2203). Hyperkalemia (serum K >5.5 mmol/L) was reported in a total of 20 patients (3.4%) in the long term study. Most elevations (in 16 patients out of 20) in potassium were transient and potassium levels returned to normal at subsequent or final visits. In three patients only on aliskiren/valsartan treatment, potassium level remained above 5.5 mmol/L while one patient on aliskiren/valsartan /HCTZ treatment had elevated potassium at the final visit (source: SPV2301 CSR Table 12-8 and PT table 14.3-2.3.

Adverse events related to renal functioning were very infrequent in placebo-controlled studies. The incidence of any AE in the renal and urinary system was lower with the aliskiren/valsartan combination (0.8%) than with either monotherapy (aliskiren, 1.0%; valsartan, 1.3%, placebo, 0.3%) [SCS-PT Table 4.1-1 and PT-Table 4.1-5].

Since patients with renal impairment are at higher risk of adverse events when receiving inhibitors of the RAAS, safety analyses based on renal function were conducted, as described in the M.A.A.

In placebo controlled studies, the incidence of adverse events in the aliskiren/valsartan combination group was similar to placebo and monotherapies across the different GFR sub-groups (For GFR < 60 group 5 patients (29.4%); for 60 ≤ GFR < 90 group: 108 patients (33.3%); for GFR ≥ 90 group: 93 patients (34.4%)). There was no increase in incidence of AEs in the patients with low GFR (GFR< 60) [SCS PT-Table 4.1-2f].

In study SPV2301, adverse events related to renal functioning occurred at a slightly higher incidence of 2.0%, reflecting the longer duration of the study [SCS-PT-Table 4.1-7]. The incidence of AEs in each GFR subgroup was similar for aliskiren/valsartan combination treatment, with lowest incidence in the patients with GFR < 60 mL/min/1.73m^2 group (23 patients (65.7%) compared tor 220 patients (70.7%) with 60 ≤ GFR < 90 group and for GFR ≥ 90 group 180 patients (70.6%)) [SCS PT-Table 4.1-6f]. There were no patients with reported AEs of renal failure, also there were no other renal disorder-related AEs reported. There was only one report of hematuria (aliskiren/valsartan treatment). There was one report of uric acid increased (0.2%) and one report of increased K^+ (0.2%). The incidence of hyperkalemia reported as an AE was low (1%) [Study SPV2301- PT-Table 14.3.1-1.1].

Monitoring the long term effect on renal function is an important safety measure for agents that inhibit the RAS system. One year of treatment with the aliskiren/valsartan combination in patients with mild to moderate renal impairment (eGFR 60 - <90 ml/min/1.73 m^2) did not result in a clinically significant decrease from baseline in eGFR. In the aliskiren/valsartan combination treatment group, the mean change in eGFR for patients with an eGFR value of 60 ≤ GFR <90 ml/min/1.73 m^2 was -0.3 compared to -0.4 in the total group. For patients with an eGFR < 60 ml/min/1.73 m^2 , an increase of 4.5 in eGFR was observed in patients treated with the aliskiren/valsartan combination and in the overall group [SCS-PT-Table 5.7-2b].

In the long term study SPV2301, few patients had a baseline GFR < 60 ml/min/1.73 m^2 (moderate or severe renal impairment). Among the 22 patients with GFR <60 treated with aliskiren/valsartan, none had creatinine values > 176.8 µmol/L and one patient had BUN values > 14.28 mmol/L; one patient had K^+ values above 5.5 mmol/L, and no patients had K^+ values ≥ 6.0 mmol/L [SCS- PT-Table 5.6-2f].

Safety by baseline renal function (est. GFR ≤ 60; > 60 to < 90; ≥ 90mL/min/1.73m^2) is also described in the Summary of Clinical Safety Section 5.1.2.

No patients in the clinical program had AEs of nephritis or nephropathy in any treatment group.

The need for control of creatinine clearance has been added to section 4.2 of the SmPC.

Hyperkalaemia based on laboratory measurements was the only adverse event reported more frequently with the combination treatment. The cases of hyperkalaemia generally resolved on discontinuation of therapy. The proposed SmPC for Rasival recommends periodic determination of serum electrolytes including potassium to manage the risk of hyperkalaemia. In addition, hyperkalaemia is listed as an adverse reaction.

In long-term safety study SPV2301, peripheral edema was reported in a total of 12 patients (2.0%), 10 of whom were receiving aliskiren/valsartan and 2 patients (1.0%) receiving aliskiren/valsartan/HCTZ treatment [SPV2301 CSR PT-Table 14.3.1-1.1].

Observed incidence rates in clinical studies are in line with the published data for ARBs and ACEi, and reporting rates for spontaneous reports did not show any increased risk of peripheral edema to the treated population.

The proposed SmPC for the aliskiren/valsartan combination has been updated in alignment with the proposed update to the Rasilez SmPC to add peripheral edema as a post-marketing AE in section 4.8 of the SmPC.

Additional data have become available from two post-marketing observational studies; 3A Registry and RATIONAL, both conducted in Germany (for further details see [3A Registry protocol] and [RATIONAL Study protocol]). The interim analyses focused on patients receiving aliskiren/valsartan combination with and without additional antihypertensive medication. Data on patients receiving treatment with aliskiren monotherapy is not yet available.

In the RATIONAL study, 222 patients received aliskiren/valsartan combination with or without other antihypertensives. Of these 222 patients, 7 patients (3.15%) discontinued from the study prematurely, out of these, 5 patients (2.25%) discontinued without any occurrence of an AE. One patient died (transitional cell carcinoma, relationship to treatment was not suspected). One patient with AE of a

pancreas carcinoma (causality not suspected) discontinued, the reason for discontinuation however was not the pancreas carcinoma. One patient with AE erectile dysfunction (relationship to treatment assessed as possible) discontinued due to the AE. The total mean exposure to the aliskiren/valsartan combination was 328.68 days for 197 patients (exposure data was not available for all 222 patients at endpoint). 190 patients were treated with aliskiren/valsartan combination for at least 6 months (≥180 days) and 64 patients for at least one year (≥330 days). The incidence of reported adverse events was low (n=9) occurring in total in 8 patients (3.6%) in the overall aliskiren/valsartan combination group (n=222 patients). None of the AEs by system organ class (SOC) occurred in more than one patient. Most of the AEs were not suspected to be related to aliskiren/valsartan combination. Out of the 9 AEs, 3 (1.35%) were classified as SAEs (death NOS, pancreas carcinoma, hypertensive crisis) in the aliskiren/valsartan combination group. For all 3 SAEs relationship to treatment was not suspected.

In the 3A Registry study, 339 patients received treatment with aliskiren and valsartan plus other antihypertensives. Disposition data was available for 335 patients. 24 out of these 335 patients discontinued treatment between baseline and the 1 year follow up. Reasons for discontinuation were not available. In the group of 39 patients who received treatment with aliskiren and valsartan only (without other antihypertensives), a total of 37 patients completed the treatment phase. Two patients discontinued treatment between baseline and the 1 year follow up. Reasons for discontinuation were not available. The total mean exposure to the aliskiren/valsartan combination was 355.3 days for 335 patients; information from the other 4 patients was not available. 320 patients were treated with aliskiren/valsartan combination for at least 6 months (≥180 days) and 222 patients for at least one year (≥360 days). No adverse events and no serious adverse events were reported in the group of patients treated with aliskiren/valsartan combination (n=39) only without other antihypertensives. In the group of patients receiving aliskiren/valsartan and any other antihypertensive medication (n=339), two deaths were reported, for both causality to aliskiren or valsartan treatment was not suspected. One patient died due to myocardial infarction, and the other patient died with invasive bladder. Twelve SAEs and 2 non-SAEs were reported in patients treated with aliskiren/valsartan and any other antihypertensive medication.

Discussion on clinical safety

The combination aliskiren+valsartan has a positive safe profile in short-term studies.

During 1-year treatment with the high dose combination, the incidence of drug-related serious AEs is as low as 1.0%. Hypotension was rare. **Hyperkalaemia** (serum K >5.5 mmol/L) was reported in a total of 20 patients (3.4%) in the long term study, whereas diarrhoea was much more incident than in short-term studies (7%). The cases of hyperkalaemia generally resolved on discontinuation of therapy. **Impaired kidney function** occurred rarely but it was more frequent during co-treatment with diuretics. In placebo controlled studies, the incidence of adverse events in the aliskiren/valsartan combination group was similar to placebo and monotherapies across the different GFR sub-groups. In the long term study SPV2301, few patients had a baseline GFR < 60 ml/min/1.73 m^2 (moderate or severe renal impairment). No patients in the clinical program had AEs of nephritis or nephropathy in any treatment group.

The need for control of **creatinine clearance** has been added to section 4.2 of the SmPC.

No patients in the clinical program had AEs of nephritis or nephropathy in any treatment group.

In long-term safety study SPV2301, **peripheral oedema** was reported in a total of 12 patients (2.0%), 10 of whom were receiving aliskiren/valsartan and 2 patients (1.0%) receiving aliskiren/valsartan/HCTZ treatment

Observed incidence rates in clinical studies are in line with the published data for ARBs and ACEi, and reporting rates for spontaneous reports did not show any increased risk of peripheral edema to the treated population.

The SmPC for the aliskiren/valsartan combination has been adequately updated in line with the recently approved update to the Rasilez and Rasilez HCT SmPC to add peripheral oedema as a post-marketing AE in section 4.8 of the SmPC.

Angioedema:
In post marketing experience of aliskiren (PSURs 1-5 of Rasilez and PSURs 1-2 of Rasilez HCT) there are cases of angioedema in patients with a history of angioedema whatever the aetiology including a previous exposition to ACE inhibitors and ARBs.

Case reports, case series, post marketing adverse reaction data and literature data demonstrate that there is some degree of angioedema-cross reactivity between the classes of RAS blocking agents. Therefore, the potential for aliskiren-induced angioedema in patients with a history of angioedema under ACE inhibitors or ARBs cannot be excluded.

Given the potential life-threatening nature of angioedema, even if the exact mechanism of angioedema induced by these medications has not been fully elucidated, these data suggest that caution should be used when initiating aliskiren therapy in patients who previously developed angioedema with ACE inhibitors or ARBs therapy.

Considering the prevalence, albeit low, of angioedema cross–reactivity described in the literature (<10%) between ACE inhibitors and ARBs (Arch Intern Med. 2004; 164:910-913; Lancet 2003; 362:772-776), and the potential for aliskiren-induced angioedema in patients with a history of angioedema under ACE inhibitors or ARBs, close monitoring is necessary to ensure that angioedema does not occur again under aliskiren. Moreover, patients with a history of angioedema in general (idiopatic or hereditary or under other medicines) may be at increased risk of angioedema while receiving a RAS blocking agent, including aliskiren. Therefore, caution and close monitoring should be recommended when aliskiren is prescribed in these cases. The issue was discussed and it was decided to update 4.3, 4.4 and 4.8 sections of the SmPC of all alikiren-containing products to reflect the above findings/considerations.

Conclusions.
Conclusions on clinical safety
The Applicant refers to the original submission studies in support of its claim for an acceptable safety profile and confirms that the proposed SmPC provides information on clinical activity to address safety e.g. checks on blood potassium. The Applicant provides information on post-marketing observational studies in DE: 3A Registry and RATIONAL: the applicant states that these studies support already-known information on safety for the proposed product.

Safety analyses based on renal function are re-assuring on "long term" (one year-treatment) effect of the aliskiren-valsartan combination, on renal function. Hyperkalaemia based on laboratory measurements was the only adverse event reported more frequently with the combination treatment. The cases of hyperkalaemia generally resolved on discontinuation of therapy.

The only conclusions that can be drawn by the registry data are that, in this setting, the use of aliskiren valsartan is extremely limited and that therefore data from the registries have limited relevance for this application. Indeed in the 3A registry only 39 out of 14,994 patients were treated with aliskiren/valsartan alone. This represents 0.26% of the overall population. In the RATIONAL registry 75 out of nearly 7000 patients received aliskiren/valsartan alone representing roughly 1% of the overall study population. **Therefore extrapolation of data from these registries is inadequate.**

In addition, the CHMP was concerned about the use of the aliskiren/valsartan combination, which is associated with a higher number of adverse events that are related to the dual blockade of RAS, such as hypotension, syncope, hyperkalaemia and renal dysfunction. These safety issues remain an issue of major concern, in particular in patients at risk for side effects that are related to inhibition of the RAS, such as elderly patients, patients with renal dysfunction, patients with diabetic nephropathy, patient using diuretics and patients with therapy-resistant hypertension. Risk is not well quantified in all of these patient groups. So far, the clinical benefits have not been shown and the add-on effect in patients who do not respond in monotherapy has not been demonstrated. The long term benefit and safety of a fixed dose combination of valsartan and aliskiren inducing dual RAS blockade, that will be almost maximal when the higher dosages are used, has not been established either. Additional efficacy and safety data are needed, including the data from patient groups described above, in order to establish a positive benefit-risk balance.

Pharmacovigilance system

The updated DDPS provided with the responses to D120 LoQ follows the recent Novartis-wide updated submitted under the worksharing procedure in September 2009. The structure of the DDPS is changed to a core DDPS, describing the Pharmacovigilance system and a product-specific addendum according to the rule governing medicinal products in EU, vol. 9A.
The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The applicant has submitted a Risk Management Plan. The document covers identified, potential and unknown risks for the use of aliskiren/valsartan fixed combination (SPV100A) in the treatment of hypertension.
The elements of the proposed plan are consistent with the recommendations made in the CHMP Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005).
In this section the EU Risk Management Plan, including Safety Specification, Pharmacovigilance Plan, need for risk minimisation measures and Risk Minimisation Plan, is assessed.
In response to the D120 LoQ the applicant has submitted an updated version of the RMP (Version3). Many changes have been implemented even not related to the questions raised.

Safety Specification

When administering aliskiren and valsartan in combination, no new safety observations have emerged from clinical trials since the last version (RMP V2) in the proposed target indication (i.e. hypertension) constituting a new risk or providing evidence of increased severity, specificity or frequency of known or potential risks already described for aliskiren or valsartan. During the original SPV100 clinical development program, based on the laboratory findings in clinical trials, an increased incidence of hyperkalemia (serum potassium >5.5 mEq/L) was reported for aliskiren/valsartan combination compared to the monotherapy aliskiren or valsartan or compared to placebo (SCS for SPV100A aliskiren/valsartan). Therefore, this finding will be reflected in the present RMP with hyperkalemia as an identified risk.

In addition to the risks for SPV100A, appropriate reference is made to the aliskiren monotherapy RMP for the important risks identified for aliskiren RMP Annex 7-SPP100A RMP and to the valsartan pediatric RMP Annex 7 in the absence of an RMP for treatment of the adult population.

Non-clinical part of safety specification
The RMP has been amended with a summary of the pre-clinical findings. However, the applicant should furthermore assess the relevance to human usage in a table for each of the identified safety concerns as per the EU RMP template (Sect. 1.1.1). Refer also to the Non clinical AR.

Clinical part of safety specification

Limitations of the human safety database

The total clinical safety database includes adverse events and clinical laboratory evaluations, and subgroup analyses. In subgroup analyses, the number of patients with severe renal impairment or who were very elderly was small and therefore these data should be interpreted with caution in such cases.
For the aliskiren/valsartan fixed combination, new safety data became available from clinical trials completed for registration.
The aliskiren/valsartan fixed combination clinical development program includes three main trials, two placebo-controlled (Study CSPP100A2327 and Study CSPP100A2203), one open-label long term safety trial (Study CSPV100A2301), supporting data from an HCT non-responder study with an arm of add-on aliskiren/valsartan (Study CSPV100A2331). Safety analyses and data from all these studies are used to support the registration of aliskiren/valsartan for the treatment of hypertension. In addition, certain safety data (deaths and serious adverse events) are also provided from five clinical pharmacology studies [SPV100A SCS-Table 1-4].

Overall, 3,520 patients were included in the aliskiren/valsartan combination clinical development program, with 1,225 being exposed to aliskiren/valsartan combination alone.
Other groups received placebo, aliskiren or valsartan monotherapy, valsartan with HCT, or aliskiren/valsartan with HCT.
In the aliskiren/valsartan group, 349 patients were exposed for at least 180 days, and 316 for at least 360 days. The key efficacy and safety trials in this development program enrolled patients ≥18 years of age with mild to moderate essential hypertension.

Regarding the issue on the small number of very elderly patients (35 patients with ≥ 75 years of age exposed to aliskiren/valsartan combinations in the clinical trials-tab.1-3) ("*…if clinical studies with an adequate number of very elderly patients have been planned in order to better characterize the safety profile of the combination therapy…")* the applicant has provided the figures of the ongoing ALTITUDE study (SPP100E2337), a long-term, placebo-controlled, double-blind, randomised cardiovascular morbidity and mortality study with safety monitored by an independent Data Monitoring Committee. Nearly half of the trial patients are over the age of 65 years (7,000 randomised patients, with the 13.5% ≥ 75 years). However, the Applicant should still specify if in ALTITUDE (SPP100E2337) or in other studies it has been planned a comparison between the incidence of relevant risks with aliskiren/valsartan combination versus aliskiren monotherapy in very elderly patients in order to exclude an increase of the adverse reactions particularly related to the concomitant actions of the two active substances on the RAS.
The synopsis of the study protocol should be submitted prior to approval.

Clinical trial exposure
In the updated RMP the Applicant has provided a frequency table for drug exposure cross-tabulated for sex and age with 10 ys age intervals, as requested by the CHMP.

Adverse Events / Adverse Reactions

Hyperkalaemia was the only adverse reaction identified for the aliskiren/valsartan combination compared to the monotherapies and placebo.
In doube blind placebo controlled short-term studies the incidence of hypertensive patients who developed hyperkalemia (serum potassium > 5.5 mEq/L at any post baseline visit) was higher in the combination treatment group (3.4%) compared with the monotherapy aliskiren (1.0%) and 2%), monotherapy valsartan (1.2%) or with placebo (21.1%). In the majority of patients the serum potassium did not exceed 6 mEq/L and the events were transient and reversible without the requirement to discontinue therapy. In long-term open label study of one year duration, the incidence of hyperkalemia was similar to the short term placebo controlled studies (3.4% in total study patients)
These findings were reflected by including hyperkalemia as an identified risk for aliskiren and valsartan monotherapy [RMP Annex 2RMP Annex 2-Rasilez®, Diovan® CDS], and the CDS and prescribing information (PI)SmPC for aliskiren/valsartan fixed combination includes hyperkalemia as an adverse reaction [RMP Annex 2-Valturna®RMP Annex 2- SPV100 SmPC].

Important Identified Risk for the aliskiren/valsartan combination

Only hyperkalemia is reported as important identified risk in the updated RMP version 3. However, dizziness or vertigo is a signal to be monitored for aliskiren and is known as an identified risk with valsartan monotherapy, but this risk is not listed in the RMP for the combination product. The applicant should update the RMP with this risk in line with the concerns expressed over additive effects with the combination product. The Applicant should also provide in the PSURs the comparative frequency of this ADR in patients treated with aliskiren or valsartan monotherapy and versus patients treated with aliskiren/valsartan fixed combination.

In addition, as both aliskiren and valsartan can induce "Decrease in haemoglobin and haematocrit" as adverse event reported in the respective SmPCs, this should be mentioned as identified risk in aliskiren/valsartan RMP, due to possible additive effect of the two active substances.

Details of important identified and potential risks - aliskiren

The current RMP v.3 has been updated, as required by the CHMP, to consider 'Renal dysfunction' and 'peripheral edema' as identified risks. The SmPC includes these two risks as adverse event in section 4.8. In addition acute renal failure has been considered under the broader heading of 'renal dysfunction'.

Therefore, for aliskiren, six important identified risks (i.e. diarrhea, rash, angioedema, hyperkalemia, peripheral edema, and renal dysfunction) and three important potential risks (i.e. colorectal hyperplasia, hypotension, ischemic colitis) of aliskiren alone and in combination with other anti-hypertensive agents have been observed and reported in the RMP v.3.

Details of important identified and potential risks - valsartan

Four important potential risks have been identified: hyperkalemia, hypotension, renal dysfunction and angioedema. Three additional risks, which are mentioned in the valsartan pediatric RMP, were omitted here as they are not considered to be risks for the adult population based upon available data (liver function test elevation and medication error) or because existing post-marketing reports do not provide evidence of a risk of anemia in the adult population.

Several potential safety issues of concern were the subject of discussion in valsartan PSUR 13 covering the reporting period 01 Jun 2006 – 31 May 2009, namely bleeding disorders/hemorrhages, hyponatremia, interstitial lung disease and muscle disorders (rhabdomyolysis and myopathies)
Based on cumulative review of the data, none of these events were considered by the applicant to alter the benefit: risk assessment for either adults or pediatrics, or to warrant inclusion in this RMP.
Based on these information mentioned in the updated version, it's considered appropriate by the CHMP to add these potential risks to the relevant valsartan sections of Rasival RMP.

Identified and potential interactions

Aliskiren

Although no specific drug interaction studies were performed with the aliskiren/valsartan combination and other drugs, the anticipated interactions are those associated with the monotherapies. Two drug-drug interactions have been identified in the clinical program for aliskiren:

1. Decrease in furosemide systemic levels (decreased AUC and maximum plasma concentration [Cmax] of furosemide; no effect on aliskiren)
2. P-glycoprotein (Pgp) inhibitors (e.g. ciclosporin, ketoconazole, verapamil) (increased AUC and Cmax of aliskiren).

Potential interactions for aliskiren include:

a. Potent Pgp inhibitors (Quinidine)
b. Moderate Pgp inhibitors: (Itraconazole, clarithromycin, telithromycin, erythromycin, amiodarone)

Valsartan

Two drug-drug interactions were identified for valsartan which are currently listed in the Company Core Data Sheet: potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium and lithium DDI.

Potential drug interactions with atorvastatin is listed in the SmPC (Sect. 4.5), but not mentioned in the RMP. A large proportion of the target hypertensive patient population is expected to be treated concomitantly and long-term with statins including atorvastatin. The applicant should discuss how this potential interaction could be studied further.

Aliskiren/valsartan

Since aliskiren and valsartan share some known adverse events, the combination could have an additive effect on them. The RMP should reflect this potential interaction

In particular, the APPLICANT should discuss potential interactions between aliskiren and ACE inhibitors and/or ARBs and update the SmPC and RMP of Rasival accordingly.

Pharmacological class effects

Because aliskiren blocks the initial step of the RAAS and it is the first in this class of direct renin inhibitors, the safety concerns observed with other medications that act on this pathway, namely ACEIs and ARBs have been considered. AEs that have been reported in association with other drugs that act on the RAAS include hyperkalemia, angioedema, cough, and changes in renal function.

Angioedema, hyperkalemia and renal dysfunction are reported as identified risks for both aliskiren and, whilst cough and interaction with NSAIDs are included in the table of pharmacological class effects.

Summary – Ongoing Safety Concerns

Table 1 Ongoing Safety Concerns for Aliskiren

Ongoing safety concerns	
Important identified risks	Diarrhoea Rash Angioedema Hyperkalemia Renal dysfunction Peripheral edema
Important potential risks	Colorectal hyperplasia Hypotension Ischemic colitis
Identified interactions	Decrease in furosemide systemic levels; Increased aliskiren systemic levels with the potent Pgp inhibitor ciclosporin A; Increased aliskiren systemic levels with the moderate Pgp inhibitors ketoconazole and verapamil
Potential interactions	Increased aliskiren systemic levels with other moderate (itraconazole, clarithromycin, telithromycin, erythromycin, amiodarone) or potent Pgp inhibitors (quinidine).
Pharmacological class effects	Cough Interaction with NSAIDs
Important missing information	Pregnancy Paediatric patients Severe renal dysfunction Reno-vascular hypertension Cardiovascular morbidity and mortality reduction.

Table 2 Ongoing Safety Concerns for valsartan

Important identified risks	Hyperkalemia, Angioedema, Renal dysfunction, Hypotension
Identified interactions	Interaction with lithium resulting in increased lithium levels Interaction with potassium-sparing diuretics resulting in increased serum potassium,
Pharmacological class effects	Interaction with NSAIDs

The applicant is requested to update the RMP in section 1.10 summary - ongoing safety concerns according to the guideline in order to classify the safety concerns as important identified risks, important potential risks and important missing information.

In the section 5-Summary of the RMP-table 5-1 submitted the applicant is requested to delete the references to the Core Data Sheet (CDS) since the CDS is not a communication document for healthcare professionals or patients.

The table 5-2 of the RMP submitted should be presented in the pharmacovigilance plan section.

Pharmacovigilance Plan

The applicant will apply the same PV activities for the aliskiren/valsartan fixed combination as those planned for aliskiren monotherapy and routine PV activities for the newly added valsartan risks.

Safety concerns and planned pharmacovigilance actions applicable for aliskiren /valsartan combination

Routine pharmacovigilance and aggregate analysis in PSURs are planned for hyperkalemia.

The applicant has committed to provide a comparative analysis of AEs observed with combination therapy as opposed to aliskiren monotherapy via the PSUR procedure. However, the PSURs should include a comparative analysis of ADRs reported for any important risk for aliskiren, valsartan and for the combination, i.e. combination therapy compared to both aliskiren and valsartan monotherapies.

The Applicant should provide a comparative table with the PSURs for the two monotherapies and the combination to assess whether or not the signal of solid tumours has been increased in the combination.

Safety concerns and planned pharmacovigilance actions applicable for aliskiren
Routine pharmacovigilance and aggregate analysis in PSURs are planned for the identified risks (hyperkalemia, diarrhoea, renal dysfunction, angioedema, Peripheral edema) and for the potential risks (Colorectal hyperplasia, Ischemic colitis). Only routine pharmacovigilance is planned for Rash (identified risk) and Hypotension (potential risk). However, the Applicant should still monitor **hypotension** events, in particular in the elderly (>65 years) who seem to be more sensitive to aliskiren than the younger generation. Even though the issue was not raised for aliskiren monotherapy, the risk could be higher for aliskiren combinations.
The applicant has also committed to keep all serious skin reactions under review in accordance with the PSUR procedure. The Applicant should submit a proposal of wording to add also to Rasival SmPC section 4.8 the adverse reactions "**SCARs**" (severe cutaneous adverse reactions) including "toxic epidermic necrolysis" and "oral mucosal reactions", as post-marketing spontaneously reported ADRs of unknown frequency.

I**schemic colitis** is now included as a new potential risk based on receipt of isolated reports in patients receiving aliskiren.

The Applicant should however discuss the need to add a warning in the SmPC advising caution in case of risk factors for ischemic colitis in particular the wording should advise to correct risk factors before aliskiren administration and to closely monitor the patient during the treatment.

As requested, colorectal hyperplasia and hypotension should continue to be monitored by aggregate analysis. the applicant should submit also in Rasival PSURs a cumulative review of cases and reporting rate of colorectal hyperplasia, colorectal neoplasms and any other neoplasms occurred with aliskiren monotherapy, valsartan and the combination, by comparing these data with the incidence of any neoplasms in the population. A comparative table should be submitted.

In the context of the discussion on the issue aliskiren and risk of **angioedema** in patients with medical history of angioedema the RMP of Rasival should be updated accordingly. In this context, the Applicant should also make a proposal for an appropriate study to explore the risks of angioedema further and to generate more accurate data on the incidence of this ADR.
The Applicant should also:
-commit to monitor cases with a medical history of angioedema/angioedema like reactions in the PSURs and a clearer definition of angioedema should be used.
-elaborate further on the underlying biological mechanism of action for angioedema/angioedema like reactions and provide such analysis for CHMP review.

The applicant has replaced their targeted questionnaires for following up AEs of important risks with check lists. All targeted follow-up material (questionnaires, check lists, etc.) for AE events or pregnancy should be submitted and agreed prior to approval. The Applicant should also explain how they plan to apply this tool.

In the proposed RMP the applicant present the safety concerns, the proposed pharmacovigilance and risk minimisation activities applicable to aliskiren/valsartan combination, applicable for aliskiren and applicable for valsartan separately. Rasival is a new FDC of aliskiren and valsartan and therefore the data should be presented together. The applicant should revised the RMP accordingly.
Important missing information**:** Pregnancy, Paediatric patients, Moderate and severe renal dysfunction, Reno-vascular hypertension, Cardiovascular morbidity and mortality reduction.

Evaluation of the need for risk minimization activities

The objective of the Risk Minimization Plan is to minimize or prevent the risks discussed in the RMP.

Risk minimization activities for fixed combination aliskiren/valsartan at the dose range (150 mg/160 mg, 300 mg/320 mg) proposed for human use for the treatment of hypertension will follow the approved plan for aliskiren monotherapy detailed in the aliskiren RMP Annex 7-SPP100A RMP and the appropriate risks from the valsartan pediatric RMP Annex 2-Diovan® CDS.

Risk Minimization Plan
Not applicable as risk minimization plan for aliskiren/valsartan consists of only routine activities.

Aliskiren Risk Minimization Plan

The risk minimization plan for aliskiren consists of only routine activities.

Valsartan Risk Minimization Plan

Currently there is no approved RMP for valsartan. However, all known adverse events of valsartan are described in the product label [RMP Annex 2-Diovan® CDS] and no additional risk minimization activities are planned.

Aliskiren/Valsartan Risk Minimization Plan

This will follow the approved RMP for aliskiren monotherapy [RMP Annex 7-SPP100A RMP] and the existing labeling for valsartan [RMP Annex 2-Diovan® CDS]. Accordingly, the risk minimization plan for aliskiren/valsartan consists of only routine activities

Summary of the risk management plan

The applicant should correct the table 5.1 of RMP following the previous comments regarding the proposed Pharmacovigilance activities and according to the SmPC (e.g. information on Verapamil interaction based also on the final negative opinion to Rasilez variation II/41-to update the SmPC)

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

Benefits

It is established that the FDC of aliskiren and valsartan (150/160 mg and 300/320 mg dose strengths) induces statistically significantly greater (though modest) reduction of systolic and diastolic blood pressure than the component monotherapies.

It is established that each active component in the scheduled dosage contributes towards efficacy.

Pharmacological-justification for the combination of the products as presented in the original submission (different and complimentary actions on the renin-angiotensin system) has been provided

Uncertainty in the knowledge about the beneficial effects

The clinical development program for the aliskiren/valsartan combination was conducted without attention to the fact that food is known to affect the bioavailability of this combination and data were not collected to assess the timing of drug administration in relation to food. Study results are also confounded by the fact that aliskiren was administered not after a light meal as per CHMP indications.

The long-term (beyond 1 year) ability of Rasival to sustain an antihypertensive effect has not been established.

The applicant has not convincingly demonstrated the minimally effective dose or the usual effective dose of the combination in the elderly (information has to be supplied in the SmPC).

There are on-going concerns that the applicant has not provided adequate data to demonstrate a statistically significant difference in blood pressure achieved between the low and higher dose combination under SmPC conditions.

The applicant's claim that once-daily dosing of a combination tablet may lead to improved compliance compared to the free combination of either one of the monotherapies, has not been demonstrated.

Extensive data on long-term (beyond 1 year) safety of Rasival are not available.

The efficacy and safety of rasival has not been established in subjects with severe hypertension (diastolic blood pressure >110mmHg, systolic blood pressure >180mmHg).

The efficacy and safety of rasival 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).
Information has been supplied in the SmPC.

The efficacy and safety of rasival has not been established in subjects with hypertensive crisis and / or hypertensive encephalopathy

The efficacy and safety of rasival has not been established in subjects with secondary hypertension

The efficacy and safety of rasival has not been established in subjects with moderate to severe renal dysfunction (information is supplied in sections 4.2 and 4.4 of the SmPC) or renal replacement therapy

Risks

Rasival use results in an increased incidence of hyperkalaemia. Information is supplied in sections 4.4 and 4.8 of the SmPC.

Rasival use may result in an increased incidence of angioedema (information has been supplied in the SmPC).

Data on the use of Rasival in children and adolescents below 18yrs, pregnant or nursing females are not available. Information is made known in the SmPC.

Owing to the valsartan component, Rasival should not be used in patients with mild to moderate hepatic impairment and is contraindicated in severe hepatic impairment and cholestasis. Information is supplied in sections 4.2, 4.3 and 4.4 of the SmPC

With reference to CHMP/EWP/240/95 Rev. 1: the possible addition of the different adverse reactions specific to each substance

Uncertainty in the knowledge about the unfavourable effects
The biological mechanisms underlying the increased risk of angioedema have not been established.

The biological mechanisms underlying the potential increased risk of solid tumours in patients treated with ARBs have not been established.

Data are not available on the use of aliskiren/valsartan in combination with any other medicine affecting the rennin-angiotensin system.

Balance
Importance of favourable and unfavourable effects
The importance of the favourable effect on blood pressure reduction cannot be adequately assessed till the uncertainties related to the food effect are solved. Being the wide therapeutic experience with the FDC not easily assessable because of the lack of predefined criteria, the insufficient data on the maintenance of the efficacy in the long term and the lack of data on efficacy in at-risk population for cardiovascular events, such as patients with severe hypertension and vascular co-morbidities, further limit the evaluation of the overall efficacy. On the same line, the importance of the favourable short-term safety is partially decreased by the paucity of data on long term safety. It is thus not possible at present to evaluate the relative weight of favourable and unfavourable factors in the absence of the food effect study on Rasival PK/PD (PRA and blood pressure) parameters.

Benefit-risk balance
The decrease in blood pressure represents an established factor in lowering the risk for cardio- and cerebro-vascular disorder, the majority of patients need more than one drug to reach the desired blood pressure. Here short-term safety has been satisfactorily demonstrated. However, it's only speculative at this point to claim that improved compliance would be present with the FDC, therefore making impossible to evaluate it in favourable effect profile. On the other hand the complexity and variability in the absorption of the FDC and thus in the bioavailability and clinical effect have not been addressed conclusively. The design of the clinical trials contains way too many uncertainties on the effect of food on the FDC. In addition, long-term (>1 years) efficacy and safety data are scarce.

Discussion on the benefit-risk assessment
The uncertainties on the different absorption criteria of the FDC and the relative effect of food should be clarified with specific studies in order to properly ascertain the pharmacokinetic and pharmacodynamic variables of either the monotherapies or the FDC. Only after this has been convincibly demonstrated can a clear assessment of the balance between efficacy and safety be performed on the aliskiren-valsartan combination.
The positive benefit-risk for each dose of the aliskiren-valsartan combination has not been adequately established in the programme of clinical trials presented and neither has the wide therapeutic experience with the use of this combination been shown.

Conclusions
The overall risk-benefit analysis is considered to be negative.

V.1 Conclusions

The overall B/R of Rasival is considered to be negative.

V.2 Package Leaflet (PL)

- User consultation

PRODUCT INFORMATION

Name of the medicinal product:	Rasival
Name and address of the applicant:	Novartis Europharm Ltd.
Name of company which has performed the user testing:	Aspect Clinical, U.K.
Type of Marketing Authorisation Application:	Centralised
Active substance:	Aliskiren/valsartan
Pharmaco-therapeutic group (ATC Code):	pending
Therapeutic indication(s):	Treatment of essential hypertension in adults. Tradename is indicated as substitution therapy only in patients already adequately controlled with aliskiren and valsartan, given concurrently, at the same dose level as in the combination.
Orphan designation	☐ yes ☒ no

- Report provided ☒ yes ☐no

- Justification for not submitting report:
  - ☐ extensions for the same route of administration
  - ☐ ref to test on same class of medicinal product
  - ☐ ref to test with same safety issues
  - ☐other *(specify)*:

- Is the justification for not submitting a report acceptable? ☐ yes ☐ no

Reasons *[assessor's views on acceptability or not of the justification – assessment of justification]*_

ASSESSMENT

	EVALUATION
CONTENT	
Consistent with SmPC	Yes, consistent with SmPC
Order as set out in article 59	Yes, compliant
Accessible language No jargon Explanations provided Active voice Good risk communication	There are numerous instances of "technical language" and elements of repetition
DESIGN AND LAYOUT	
Writing Style Simple language Short sentences Use of bullets	There are numerous instances of "technical language" and elements of repetition. Section 4 would be improved by use of bullet points (section 4 is presented in paragraph style without the use of layout to divide information).
Type face font size italics/underlining capitals/lowercase	Capitals are used in section headings There is one use of bold + italic (in paragraph on pregnancy)
Layout Spacing White space ContrastLeft justified Columns	The applicant has presented the PIL in "landscape" style and as a long, thin strip of paper. There is much "white space" at the end of the PIL The PIL mock-up is black & white, no colour: there is sparing use of bold font within the body of the text: bold font is used in headings.
Headings Consistent location Stand out	Headings stand out (use of bold and larger font size) Section 4 is the only heading that does not start at the top of the page
Use of colour Present Adequate contrast	n/a
Symbols and Pictograms	The Novartis symbol appears at the top of the PIL
ASSESSMENT OF USABILITY TEST RESULTS	
KEY SAFETY MESSAGES All safety messages identified	
REVIEW OF PROTOCOL Selection of participant Sex/age profiles Numbers Appropriate patient experience PIL actual size and layout as in finished pack	Standard inclusion / exclusion criteria are described on page 11 of the submitted report. There were 25 participants in the pilot and subsequent 2 rounds of testing Detailed demographics are supplied on page 18 of the report: participants had a broad range of educational achievements: all were Caucasian: the average age was 44yrs (this may be considered lower than the age of the target population). Although the maximum age recorded was 70yrs, the average suggests that this was an exception (and the introduction to the test states that the target audience was up to 80yrs). The PIL mock-up is presented (it is understood that this was the PIL that was used in the user-test: the applicant is requested to clarify) The PIL wording was changed before and after round 1 in response to analysis of results of questioning: this is acceptable
QUESTIONS ASKED AND	The questions asked are presented on page 16 of the report: the order

MODEL ANSWERS Random order Key safety issues addressed Record of participant responses General impressions of the leaflet	of questions (as shown by the applicant) appears to conform to the order/layout of the PIL i.e. not entirely random. Question 14 is: "how many people are likely to get hyperkalaemia?". It is considered by this assessor that "hyperkalaemia" is a technical term that few people would understand: it is remarkable that 90% of participants were able to find and understand the answer. Verbatim responses are not supplied but at least one subject recorded "Hyperkalaemia? What is it?" Key safety issues on allergy, pregnancy and selected adverse events are addressed The interview recorded the responses of participants in a semi-quantitative manner as described on page 15 of the report. Participants views are recorded: at the end of round 1, it is noted that comments are mostly unfavourable (table 5, page 24: "type face too small", "medical terms used", "long winded" etc. Although the comments at the end of round 2 are more favourable, there are still comments such as "medical words", "long words", "lot of medical information".
EVALUATION OF RESULTS Does the evaluation cover location and understanding of the information as separate pieces of data Are participants required to put information into their own words Describe question rating system How are data presented	Interviews took (about) 20mins. Location and understanding were tested. The interview recorded the responses of participants in a semi-quantitative manner as described on page 15 of the report. A full example of how results were recorded is shown on pages 98 onwards. The (apparently) better results of round 2 may reflect the participant mix: round 1 contained students and attendants whilst round 2 contained managers and a retired teacher i.e. apparently higher educational achievement of participants in round 2. The applicant has presented combined data from rounds 1 & 2 as a histogram (individual round histograms are not presented).
DISCUSSION OF MODIFICATIONS MADE AS A RESULT OF TESTING Consider any problem areas How have these been addressed Are any recommendations not taken forward	The PIL wording was changed before and after round 1 n response to analysis of results of questioning: this is acceptable. Results of round 2 were similar to round 1 (after which the wording of the PIL was modified) It is considered that the proposed PIL contains numerous instances of technical language. The applicant may have considered that further simplification after round 2 was warranted.
ASSESSMENT OF "BRIDGING STUDY" TO JUSTIFY ABSENCE OF TESTING	n/a
CONSIDER WHICH ASPECTS ARE RELEVANT Similar or lesser safety issues to be communicated Same drug class Same patient population Line extension Same pharmaceutical form Same layout and format of PIL	n/a

OUTSTANDING POINTS

PIL content:

The applicant is requested to

- give information on the font(s), font size(s) and colours used in the final PIL.
- give assurance that the font(s) and font size(s) comply with the Guideline on Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use, ENTR/F/2/SF/jr (2009)D/869, Brussels, Jan 2009

User test:

The applicant is requested to

- clarify that the PIL used in the 2nd round of the user-test is the final, proposed PIL for this application
- give information on how participants were selected / volunteered
- give information on the setting of the PIL user-test
- comment on the sequence of questions and discuss if the sequence was random
- comment on the mix of participants of round 2 versus round 1 and discuss if this may have contributed to the apparently better outcome of round 2 versus round 1 (round 2 participants had apparently higher educational achievement)

CONCLUSION
The submitted PIL user-test is in compliance with article 59(3) of EU Directive 2001/83/EC as amended. The applicant claims that the results of the PIL user-test demonstrate that the subject can find, understand and act on information in the PIL.

There is concern that:
(a) the order of questions (as presented on page 16 of the submitted report) appears to conform to the order/layout of the PIL i.e. the order of questions appear not to be random. The applicant is requested to clarify how the order of questions was reached and to affirm that questions were "posed in a random manner".
(b) the testing procedure has not fully addressed the ability of subjects to understand information (such as "hyperkalaemia") and taken steps to correct such issues of technical language
(c) the (apparently) higher educational achievement of subjects in round 2 gives an erroneous impression of an improved PIL i.e. subjects more able to understand complex issues.

The proposed PIL may be acceptable if the applicant submits acceptable responses to the questions / outstanding points.

On the grounds of improved safety, changes to the wording of the PIL are recommended (changes are mostly to address issues of technical language and repetition): refer to PIL assessment.