European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT

FOR

Exforge HCT

International Nonproprietary Name: amlodipine besylate / valsartan / hydrochlorothiazide

Procedure No. EMEA/H/C/001068

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Novartis Europharm Limited submitted on 4 September 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Exforge HCT, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 19 March 2008.

The legal basis for this application refers to:

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

The applicant applied for the following indication: "Treatment of essential hypertension. Exforge HCT is indicated as replacement therapy in patients whose blood pressure is adequately controlled on amlodipine, valsartan and hydrochlorothiazide (HCT) used as individual or combination therapies".

Information on Paediatric requirements
Pursuant to Article 7, the application included an EMEA Decision P/58/2008 for the following condition:

- Essential hypertension

on the granting of a (product-specific) waiver.

Scientific Advice
The applicant received Scientific Advice from the CHMP on 19 July 2008 and 31 August 2008. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status:
A new application for Exforge HCT was filed in the following countries: USA and Switzerland.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: **Steffen Thirstrup** Co-Rapporteur: **Alar Irs**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 4 September 2008.
- The procedure started on 24 September 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 December 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 December 2008.
- During the meeting on 19-22 January 2009 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 January 2009.
- A clarification meeting with the Rapporteurs on the CHMP List of Questions was held on 5 February 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 March 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 May 2009.
- During the CHMP meeting on 26-29 May 2009 the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 22 June 2009.

- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 7 July 2009.
- During the meeting on 20-23 July 2009 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Exforge HCT on 23 July 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 July 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Hypertension affects approximately 1 billion subjects worldwide and the prevalence in Europe has been estimated to be approximately 44%, in some countries reaching up to 55%. Uncontrolled hypertension is seen as a major health risk, increasing the probabilities of myocardial infarction, heart failure, stroke, kidney disease and other severe conditions. The 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has recommended that blood pressure be reduced below 140/90 mmHg when treating hypertensive patients in general, and to even lower levels (<130/80 mmHg) in patients with serious concomitant conditions such as diabetes and chronic kidney disease. The hypertension guidelines issued by the European Society of Hypertension and European Society of Cardiology give similar targets.

Monotherapy is rarely sufficient to normalise blood pressure. Data from clinical trials indicated that after 5 years of patient follow up, the percent of patients with controlled blood pressure was 66%; however, 63% of patients required administration of three or more antihypertensive drugs and 27% of patients required four or more antihypertensive drugs. Poor treatment effect in real life conditions can be attributed to multiple factors, including among others poor compliance with medication and underutilisation of effective drug combinations. Fixed combination antihypertensive agents represent a therapeutic alternative to high dose monotherapy or to free combinations of multiple drugs. A potential advantage of fixed dose combination therapy is improved patient compliance by reducing the multiple pill load and simplifying the treatment regimen, although the clinical relevance of this assumed benefit has been clearly established.

The currently presented triple combination of valsartan, an angiotensin receptor blocker (ARB), amlodipine, a calcium channel blocker (CCB), and hydrochlorothiazide, a thiazide diuretic, could be an appropriate choice for management of some forms of hypertension as the mechanisms of action of the three drugs are complementary. Hydrochlorothiazide is a diuretic that produces smooth muscle cell relaxation and volume depletion. Hypokalaemia is a known side effect of thiazide diuretic therapy. The addition of an ARB to a thiazide diuretic has a potentially synergistic effect on blood pressure reduction by blocking the actions of angiotensin II at the AT1 receptor and also attenuates diuretic-induced hypokalaemia. The addition of a dihydropyridine calcium channel blocker, which is an arterial vasodilator, reduces blood pressure further. Apart from this, the ARB has the potential to diminish the peripheral oedema known to occur with dihydropyridine CCBs by providing both arterial and venous vasodilatation.

Valsartan (VAL) monotherapy was first developed for the treatment of hypertension and has been marketed in Europe in doses of 80-160 mg since 1996 and in the highest dose of 320 mg since 2006. Valsartan has also been approved and marketed for the treatment of patients with chronic heart failure since 2002 and patients with post-myocardial infarction since 2005 in total daily doses up to 320 mg. Valsartan has also been marketed in Europe as a fixed combination with hydrochlorothiazide and with amlodipine (AML) since 1998 and 2007, respectively.

Amlodipine monotherapy is approved for the treatment of hypertension and angina, and in some countries for angiographically documented coronary artery disease and is available in doses of 5 and 10 mg. In some countries, amlodipine is used once daily in 2.5 mg doses for special patient populations.

Hydrochlorothiazide (HCT) monotherapy has been marketed since 1959 and is approved for the treatment of hypertension and oedema. It has been used alone or in combination with other antihypertensive agents in once daily doses of 12.5 -25 mg.

In Europe, the fixed-dose combination of VAL/HCT has been marketed for hypertension at the lower doses of VAL since 1998 and at the higher dose of VAL 320 mg in combination with HCT since 2007.

The fixed combination of VAL/AML with doses of VAL 80 and 160 mg has been marketed for hypertension in Europe since 2007.

The claimed indication is:
Treatment of essential hypertension.
Exforge HCT is indicated as replacement therapy in patients whose blood pressure is adequately controlled on amlodipine, valsartan and hydrochlorothiazide (HCT) used as individual or combination therapies.

The approved indication is:
Treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual-component and a single-component formulation.

2.2 Quality aspects

Introduction

Exforge HCT is a fixed combination medicinal product, containing three active substances: amlodipine (as the besylate salt), valsartan and hydrochlorothiazide, and is presented as film-coated tablets. Five strengths have been developed. The tablets contain 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg or 10/320/25 mg of amlodipine, valsartan and hydrochlorothiazide, respectively.

The tablet core contains besides the active substances the following excipients; cellulose microcrystalline, crospovidone, colloidal anhydrous silica and magnesium stearate. The tablet coating contains hypromellose, macrogol 4000 and talc and one or more colorants. The colorants used depend on the tablet strength and are titanium dioxide, yellow iron oxide or red iron oxide. The medicinal product is packed in PVC/PVDC blisters.

Active Substance

Amlodipine besylate
Amlodipine is the INN for the chemical substance 3- Ethyl- 5- methyl (4RS)- 2- [(2-aminoethoxy) methyl]- 4- (2- chlorophenyl)- 6- methyl- 1, 4- dihydropyridine- 3, 5- dicarboxylate benzenesulphonate (anhydrous substance). The molecular formula is $C_{26}H_{31}ClN_2O_8S \cdot C_6H_5SO_3H$ and the relative molecular mass 567.06 g/mol. There is a monograph for amlodipine besylate in the Ph. Eur. The active substance is well known and has been adequately characterised. It is a white or almost white powder. The racemic mixture of R and S isomers is used. It is slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol and slightly soluble in 2-propanol. There is no solid-state polymorphism of amlodipine besylate described in the literature.

• Manufacture
Amlodipine besylate drug substance is supplied by three manufacturers. Certificates of suitability (CEP) for manufacturing and control of the drug substance have been provided for the three manufacturers.

• Specification
Amlodipine besylate from each supplier is controlled according to the requirements of the Ph. Eur. monograph with additional requirements as stated on the CEP. The satisfactory quality is generally ensured through the CEP. However, in addition to these tests the MAH included additional tests in his drug substance specifications. These test include tests for particle size (laser light diffraction), identification (X-ray powder diffraction), heavy metals (ICP/OES), residual solvents (GC), specific limits for any impurity other than those mentioned in the Ph.Eur monograph (HPLC) and a microbial

limit test (plate count method). Adequate validation of the additional in-house methods has been performed.

• Stability
Only one drug substance supplier has a retest period included in the CEP. The other two suppliers provided long-term and accelerated stability data in order to establish an acceptable retest period.
At one manufacturer, amlodipine besylate batches have been stored at 25°C/60% RH for 9 months and at 40°C/75% RH for 6 months in simulated commercial packaging. For this manufacturer, the MAH committed to test the drug substance each time before use in the drug product until a re-test period has been established.
At the other manufacturer batches have been stored at 25°C/60% RH for 12-18 months and 40°C/75% RH for 6 months in simulated commercial packaging. For this manufacturer, the proposed re-test period was found acceptable.
Both manufacturers tested the following parameters in their stability studies: appearance, related substances by HPLC, water content and assay by HPLC. Optical rotation was checked additionally by one supplier. No significant changes were seen during storage. All results complied with the specifications at both long term and accelerated conditions.

Active Substance
Valsartan
Valsartan is the INN for the chemical substance (S)-2-{N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-amino}-3-methyl-butyric acid. The molecular formula is $C_{24}H_{29}N_5O_3$ and the relative molecular mass 435.5 g/mol. There is no Ph. Eur. monograph for valsartan. Valsartan is a white to practically white, fine powder, melting at 105-110 °C with decomposition. Its solubility in water is 0.18 mg/ml and in 0.1N HCl 0.084 mg/ml.
There is one chiral centre in the valine moiety of the molecule but essentially the pure (S)-enantiomer is used. The assigned (S)-configuration is defined from the synthetic origin ((L)-valine).
Its optical activity is [α]D/20 = -67±1° in methanol. X-ray powder analysis rated valsartan samples as poorly crystalline. No solid-state polymorphism is known to exist for valsartan.

• Manufacture
The manufacturing route comprises five consecutive synthetic steps and two auxiliary steps for reagent preparation. Purification is achieved by recrystallisation. The synthesis process of valsartan is well known and has been used for many years. Only slight modifications have been made to further improve the quality.
No process validation is necessary as the synthesis is well established and the substance does not undergo aseptic processing or sterilization.
Adequate in process controls are in place and appropriate specifications have been adopted for the starting materials, solvents, reagents and auxiliary materials. All relevant impurities (related substances, degradation products) and residual solvents have been appropriately characterized.

• Specification
The valsartan specification includes tests for appearance (visual examination), absorbance (420 nm), clarity of the solution in methanol, particle size (laser light diffraction), identity (IR, HPLC), enantiomer (HPLC), residual solvents (GC), water content (KF), sulphated ash, heavy metals (X-ray fluorescence), assay based on anhydrous and solvent-free substance (HPLC, titration), related substances (HPLC), and microbial limit test (plate count method). Appropriate justification of the specifications for valsartan has been provided.

• Stability
13 production scale batches have been stored at 25 °C /60 % RH for up to 36 months. In addition 7 of these batches have been stored at 30 °C /60 % RH, for up to 9 months and at 40 °C /75 % RH up to 6 months in the proposed market packaging. In addition, another 3 batches from an alternative manufacturing site have been stored at 25 °C /60 % RH for 36 months and at 40 °C /75 % RH for 6 months in the proposed market packaging. The following parameters were investigated: appearance, assay and related substances, specific rotation in methanol, clarity of solution in methanol, absorbance

and water. It can be concluded that valsartan is very stable. All batches comply with the proposed specification at all storage conditions. The proposed retest period is considered acceptable in the proposed containers, without special requirements for storage.

Active Substance
Hydrochlorothiazide

Hydrochlorothiazide is the INN for the chemical substance 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. The molecular formula is $C_7H_8ClN_3O_4S_2$ and the relative molecular mass 297.74 g/mol. There is a Ph. Eur. monograph for hydrochlorothiazide. Hydrochlorothiazide is a white to almost white powder, melting at 263-275 °C. It is very slightly soluble in water and in 0.1N HCl. It doesn't possess an asymmetric center and is therefore non-chiral. It exists in only one, optically inactive form. Hydrochlorothiazide does not absorb water at relative humidity below 97% at 23°C. Polymorphism is known to exist for hydrochlorothiazide.

- Manufacture

Hydrochlorothiazide drug substance is supplied by two manufacturers. A certificate of suitability (CEP) for manufacturing and control of the drug substance has been provided for one manufacturer.
For the second manufacturer, adequate information about the manufacturing, control of materials and control of critical manufacturing steps has been supplied in the form of an active substance master file (ASMF). The commercially available hydrochlorothiazide is further purified by the MAH. Appropriate specifications have been adopted for the starting materials, solvents, reagents and auxiliary materials. All relevant impurities, degradation products and residual solvents have been appropriately characterized.

- Specification

The drug substance manufacturer's specifications comply with the Ph Eur monograph. However, in addition to these tests the MAH applies in-house specifications. These include tests for appearance (visual examination), clarity and absorbance of the solution in dimethyl sulfoxide, particle size (air-jet sieving), consumption of NaOH and HCl (colouration), identity (IR, UV), assay and related substances (HPLC), residual solvents (GC), organic volatile impurities, loss on drying, sulphated ash, heavy metals (sulphide precipitation, AAS) and microbial limit test (plate count method). All specifications are considered adequate and the analytical procedures have been satisfactorily described and validated in accordance with the ICH guidelines. The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data have been presented and all batches were in compliance with the predefined active substance specification.

- Stability

One hydrochlorothiazide manufacturer has a re-test period included in the CEP. The second hydrochlorothiazide manufacturer provided long-term and accelerated stability data in order to establish an acceptable retest period. Three production scale batches have been stored at 25°C/60% RH for 48 months and at 40°C/75% RH for 6 months in the proposed market packaging.
The following parameters were investigated: characters, acidity, chlorides, related substances, loss on drying, sulphated ash and assay. No significant changes are seen during storage at either long-term or accelerated conditions. Additionally, the hydrochlorothiazide manufacturer performed a forced degradation study on 3 batches. These were stored at 80°C for 10 days. No significant changes were seen.
Furthermore, the MAH has performed stability studies under long term (5 years) and accelerated (6 months) conditions on eight batches micronised hydrochlorothiazide. The following parameters were investigated: appearance, clarity and absorbance of solution in dimethyl sulfoxide, consumption of NaOH and of HCl (colouration), loss on drying, related substances (TLC, HPLC) and assay (titration, HPLC). It was concluded that the retest period proposed for hydrochlorothiazide, micronized is considered acceptable in the proposed containers, when protected from light.

Medicinal Product

- Pharmaceutical Development

The aim of formulation development was to develop an immediate release tablet combination product that would be bioequivalent to the marketed medicinal products containing each drug substance individually.
The development of Exforge HCT was based upon the formulation and manufacturing process of the already authorized amlopidine/valsartan and valsartan /hydrochlorothiazide film-coated tablets, because of the applicant's extensive knowledge of these formulations. The drug product is presented as ovaloid, biconvex film coated tablets (white, yellow or brown-yellow). Five formulations have been developed, containing 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg or 10/320/25 mg of amlodipine, valsartan and hydrochlorothiazide, respectively.

During the development phase, the MAH evaluated adequately the compatibility of the three active substances by intermixing followed by storing. The excipients selected for Exforge HCT are standard ingredients in tablet formulations, and meet the Ph. Eur requirements. The concentration of each excipient is within the usual range of application. The compatibility of the drug substances with the excipients has been investigated during the development of the film-coated tablets; stability has been demonstrated.

The tablet cores are coated with a non-functional coating to provide a distinctive tablet colour to aid in the identification of assorted tablet strengths and to mask the slightly bitter taste of the valsartan drug substance. The basic coating premixes (yellow, white and red) are a combination of ingredients established for use in medicinal products. A monograph for the premixes themselves does not appear in any pharmacopoeia; however, the basic coating premix ingredients meet compendial requirements and international standards.

Two bioequivalence studies have been performed. The studies determined the relative bioavailability of the 5/160/12.5 mg and 10/160/25 mg amlodipine/valsartan/HCT film-coated tablets with the corresponding doses used in the pivotal safety/efficacy trial. For the three other strengths, 5/160/25 mg, 10/160/12.5 mg and 10/320/25 mg, comparative dissolution data has been provided to support the biowaivers.

Comparative dissolution profiles for amlodipine besylate, valsartan and hydrochlorothiazide drug substances were obtained with Exforge HCT film-coated tablets in three different media, pH 6.8 (phosphate buffer), pH 4.5 (acetate buffer) and pH 1.0 (0.1N HCl). The dissolution tests were performed using USP apparatus 2 (paddle) at 50 rpm. For the 10/320/25 mg strength dissolution was carried out at 50 rpm and at 55 rpm. Adequate justification has been provided to support the dissolution conditions. Dissolution profiles and f2 similarity factors were calculated for each combination of tablets tested (5/160/25 mg vs. 10/160/25 mg, 10/160/12.5 mg vs. 5/160/12.5 mg and 10/320/25 mg vs. 5/160/12.5 mg). In all cases the similarity factor was between 50 and 100 suggesting that the dissolution profiles are similar.

- Adventitious agents

None of the excipients are of human or animal origin, therefore there is no BSE/TSE risk.

- Manufacture of the Product

The process used for the manufacture of Exforge HCT film coated tablets is based on the marketed medicinal products containing valsartan, valsartan/hydrochlorothiazide and valsartan/amlodipine, which are presented as mono-layer film-coated tablets. The manufacturing process is a standard dry granulation process including pre-blending, roller compaction, screening, final blend, compression and film coating. The manufacturing process has been demonstrated to be robust and to produce a finish product of the desired quality within the agreed finished product specification.

- Product Specification

The specification for Exforge HCT includes tests for: appearance (visual examination), identification of amlodipine, valsartan and hydrochlorothiazide (TLC, HPLC), identification of colourants (colour reaction), dissolution (HPLC), water, degradation products of amlodipine, valsartan and hydrochlorothiazide (HPLC); assay for amlodipine, valsartan and hydrochlorothiazide (HPLC), uniformity of dosage units (Ph. Eur), and Microbial limit tests.
All tests included in the specification have been satisfactorily described and validated, according to the state of the art. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Batch analysis results comply with the proposed specification and confirm consistency & uniformity of manufacture and indicate that the process is under control

- Stability of the Product

Three pilot scale batches of each strength have been stored at long term conditions (25ºC/60% RH for 18 months), at intermediate conditions (30°C/65% RH for 18 months) and at accelerated conditions (40ºC/75% RH for 6 months) in the proposed market packaging (DPX blisters and alu-alu blisters).
The parameters investigated were: appearance (visual examination), water content (KF), dissolution (HPLC), assay and related substances for amlodipine, valsartan and hydrochlorothiazide (HPLC) and microbial limits test.
At long term and intermediate conditions no significant changes were seen during storage for 18 months. The degradation products were seen in a level of not more than the reporting level of 0.1%, neither the assay did change during storage. The dissolution did not change during storage for any of the active substances.
At accelerated conditions no significant changes in assay values, degradation products nor in dissolution were observed within the first three months. In the DPX blisters, however, significant water absorption was observed as DPX packaging offers the least resistance to moisture permeation. As Exforge HCT tablets are known to be hygroscopic, the film coating can crack due to tablet expansion.
In addition, a photostability study has been carried out with each tablet strength, in which it was shown that the tablets are sensitive to light. However, it has been demonstrated that the proposed blister packaging adequately protects the finished product from light.

On the basis of the provided data, the proposed shelf life and storage conditions, as stated in the SPC, are acceptable.

Discussion on chemical, and pharmaceutical aspects

The quality of Exforge HCT is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. There are no major deviations from EU and ICH requirements.

The synthesis of the active substances amlodipine besylate, valsartan and hydrochlorothiazide is adequately described and impurities are characterised, in line with current ICH guidelines. The manufacturing process of the medicinal product Exforge HCT is under control and ensures both batch to batch reproducibility and compliance with standard procedures and specifications. The analytical methods have been validated and ensure consistent quality of the active substance and the finished product. Certificates of Suitability and stability data on the active substances support the proposed re-testing period, and the stability data on the finished product support the shelf life as stated in the SPC.

In conclusion, information on development, manufacture and control of the active substance and medicinal product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the Opinion there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant signed a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

2.3 Non-clinical aspects

Introduction

Exforge HCT is a new medicinal product for the treatment of hypertension, which combines a well known and marketed calcium channel blocker amlodipine, an angiotensin II receptor antagonist valsartan (VAL), and a thiazide diuretic hydrochlorothiazide (HCT). The guideline on the non-clinical development of fixed combinations of medicinal products (CHMP/SWP/258498/2005) concludes that additional animal studies are generally not needed if there is sufficiently documented clinical experience, although some aspects may still need to be addressed. No primary pharmacodynamic studies were conducted with valsartan, amlodipine and hydrochlorothiazide as triple combination product. This is deemed acceptable as the combinations VAL/AML and VAL/HCT showed sufficient additive effects *in vivo*, HCT has been used as a diuretic for a substantial time and the VAL/AML/HCT combination therapy is also anticipated to be additive due to the complementary mechanisms of action of the three drug classes.

Pharmacology

- Primary pharmacodynamics

Reference was made to literature suggesting the additive effect of HCT and/or AML, and/or VAL on the blood pressure in spontaneously hypertensive rats (SHR).

In the first study combination of 4 mg/kg/day of AML and 10 mg/kg/day of VAL caused a similar decrease in blood pressure as 8 mg/kg/day of AML or 20 mg/kg/day of VAL when the drugs were used separately. Another study evaluated progression of diabetic nephropathy in streptozoticin treated SHR. Following the induction of diabetes, the animals were treated with VAL, AML, verapamil, or combinations of VAL with AML or verapamil for 32 weeks. VAL (30 mg/kg/day), AML (6 mg/kg/day), and a combination of VAL/AML (20/4 mg/kg/day) caused a similar reduction of the blood pressure. However, only VAL as monotherapy had any effect on progression of the nephropathy. Thus, blockade of the renin-angiotensin system is superior to calcium channel blockade to retard the development of albuminuria and it is debated whether there is a threshold of renin-angiotensin system blockage necessary to achieve renal protection. Although the main rationale for VAL/AML/HCT combination must be derived from clinical experience, the CHMP questioned the preclinical findings reported in the diabetes induced rats treated with the combination of VAL and AML and questioned whether this combination is a suitable alternative for the treatment of hypertension in diabetic patients. In response it was argued that although there is no original study specifically studying this triple combination in hypertensive patients with diabetes, it is possible to derive clinical data from other clinical study that included this subpopulation. These suggest that VAL/AML/HCT may be a suitable for the treatment of hypertension in diabetic patients. In addition, the screening safety data for new signals is proposed by means pharmacovigilance programme in order to handle possible VAL/AML/HCT adverse effects in clinical practice.

Further non clinical testing tested VAL alone or in combination with HCT administered continuously to SHRs. VAL given at doses of 1 and 3 mg/kg/day, showed significant, dose-dependent reductions in mean arterial pressure. Treatment with HCT (3 and 10 mg/kg/day) also significantly lowered the mean arterial pressure, but this response was not dose-dependent. Additive blood pressure-lowering effects were observed when a low dose VAL (1 mg/kg/day) was co-administered with either dose of HCT (3 and 10 mg/kg/day). The effect of chronic combination therapy using VAL and AML has been assessed previously; a 6-week and a 32 week study in the SHR model showed additive lowering effect of VAL and AML on blood pressure. Overall, the above-referenced studies in the SHR models clearly demonstrated additive lowering effect on blood pressure.

- Secondary pharmacodynamics

No secondary pharmacodynamic studies have been conducted with the combination of VAL/AML/HCT. This is acceptable due to the clinical experience with the individual compounds and the double drug combinations.

- Safety pharmacology programme

No safety pharmacology studies have been conducted with the combination of VAL/AML/HCT. This was considered acceptable due to the clinical experience with the use of the individual compounds. Although the evaluation of cardiovascular safety end point could have been included into the bridging toxicity study, this was conducted in rodents (see section Toxicology) and thus, the inclusion of cardiovascular safety end point is not relevant for human safety assessment.

- Pharmacodynamic drug interactions

No pharmacodynamic interaction studies have been conducted with VAL/AML/HCT combination. It is acceptable since the three compounds in the combination are well known due to sufficient clinical experience and the additive effects of the compounds are the intention of the combination.

Pharmacokinetics

Valsartan/Amlodipine/Hydrochlorothiazide

The pharmacokinetics of the triple combination has not been specifically investigated in animal ADME studies but has been characterised and compared to single drug treatment in a 13-week toxicity study in rats. Even though differences in pharmacokinetics/toxicokinetics could not be completely excluded in the 13-week toxicity study (see the Toxicology section), the lack of pharmacokinetic interactions between the three compounds in the triple combination has been confirmed by clinical data. No further non-clinical investigations are requested. A brief summary of the pharmacokinetic properties of the individual components is provided.

Absorption and Distribution

Amlodipine: Oral doses of AML were well absorbed in mice, rats and dogs, and were gradually but nearly completely absorbed in man. In healthy adult volunteers following a single oral dose of 15 mg ^{14}C-labeled AML, appearance of AML and total drug-related material in the plasma was gradual with peak concentrations attained around 6-9 hours. The absolute oral bioavailability was comparatively high in humans (64%), dogs (88%), mice (100%) and rats (100%). There was no influence of food on the absorption or bioavailability of AML in humans. AML is highly bound to human plasma proteins (>94% in rats, dogs and humans) and highly distributed into tissues with a large volume of distribution around 21-32 l/kg across species.

Valsartan: Valsartan is absorbed to a moderate extent (41%) in rat. The extent of absorption in marmoset and human was similar, but is not exactly known. Exposure to VAL increased dose-dependently and partly dose-proportionally. VAL was highly bound to proteins of plasma (>90% in several species including rats and humans). In humans, the steady-state volume of distribution of VAL after intravenous administration was small (17 l), indicating that VAL does not distribute into tissues extensively. This also confirmed the results of the radiolabelled distribution studies conducted in rats, since high levels of radioactivity were observed in blood, plasma, liver and kidneys with only low levels in all other investigated organs. VAL and/or its metabolites pass through the placental barrier of the pregnant rat. Distinct uptake of VAL and/or its metabolites in rat's mammary glands were consistent with the observed excretion into the milk of lactating rats.

Hydrochlorothiazide: Hydrochlorothiazide was well absorbed in animal species and humans, and was largely excreted in unchanged form in urine. Systemic exposure (AUC, C_{max}) in human was dose-proportional within the therapeutic dose range. Absolute oral bioavailability was 65% to 75%. Food reduces the bioavailability of HCT by approximately 10% and the C_{max} by 20% and increases the t_{max} from 1.6 to 2.9 hours.

In humans, the pharmacokinetics of VAL, HCT and AML have been well characterised when administered alone or when administered as the double combinations (VAL/HCT or AML/VAL), or when administered as the triple combination (AML/VAL/HCT).

Metabolism
Amlodipine: In animals and humans, AML was eliminated mainly through extensive, though slow metabolism and with low first pass extraction. Metabolism was catalyzed mainly by hepatic CYP3A4 and was similar in rats, dogs, mice and humans. No metabolite showed significant calcium channel antagonist activity. Only a small fraction of the dose (up to 5%) was recovered in the urine as unchanged drug. In human, rat and dog, the first step of metabolism was oxidation of the dihydropyridine ring of the racemic compound to the pyridine analogue. Further metabolism involved oxidation/hydrolysis of the side-chain ester(s) and oxidation/degradation of the amino-ethoxymethyl side chain.

Valsartan: The oxidative *in vivo* biotransformation in rats, dogs, marmosets and humans is limited. VAL is predominantly excreted unchanged in urine and faeces of all species including humans. The metabolites present in the excreta include the tetrazole-N-glucose conjugate and the tetrazole biphenyl methanoic acid derivative in mice, and the 4-hydroxy-pentanoyl metabolite in marmosets, which is the same as the one seen in humans. Two metabolites were detected in the rat liver. Each accounted for less than 8.4% of the radioactivity in the liver 8 hours after dosing. One of these metabolites was acyl glucuronide.

Hydrochlorothiazide: In humans, HCT is not metabolized to a relevant degree and >95% of the dose is excreted unchanged in urine.

In summary, metabolism of VAL and AML has been sufficiently investigated for each compound individually. As HCT is only metabolised in humans to a limited degree (<5%), animal additional metabolic studies are not considered necessary.

Excretion
Amlodipine: In rats, 33-38% of the dose can be recovered in the urine and 58-60% in faeces. In both male and female dogs, 38-51% of the dose is recovered in the urine and 38-49% in the faeces. The recovery of radioactivity in urine and faeces was similar after both oral and intravenous administration, indicating good absorption of the drug from the gastrointestinal tract. Overall, dose recovery was 91-98% in rats and 85-91% in dogs within seven days of dose administration.

Valsartan: In rats, 94%-97% of the dose was recovered in the faeces. VAL has also been shown to undergo enterohepatic recirculation in dogs. The renal excretion of VAL-related radioactivity was more pronounced in marmosets (up to 16% of the dose) than in rats (less than 2.5% of the dose). In all species investigated VAL was mainly excreted unchanged. The mechanism of the hepatobiliary elimination of VAL, which is a di-anion at physiological pH, was investigated in normal and mrp2-deficient rats *in vivo* Tr-rat and EHBR rat. VAL elimination with bile depended to about 50% on the presence of canalicular mrp2 (cMOAT) and it was shown to be a substrate of mrp2. At least an additional ATP-dependent transporter, probably of the mrp family contributes to elimination. VAL did not interact with bile acid transport or with Pgp (mdr1). Using transfected cells, VAL was shown to be a substrate of the hepatic uptake transporters OATP1B1 and OATP1B3.

Hydrochlorothiazide: Orally administered HCT is excreted largely unchanged in the urine of animals. In humans, >95% of the absorbed HCT was excreted in urine within 4 days. The drug is secreted from the renal proximal tubules after cellular uptake by basolateral organic anion transporter-1 (OAT1).

Pharmacokinetic drug interactions
Amlodipine: Amlodipine is eliminated mainly through metabolism by hepatic CYP3A4. Potentially, co-medications might interact with AML by inhibition or induction of CYP3A4. Conversely, AML might interact with co-medications, via CYP isoenzymes involved in their metabolism. In *in vitro* studies using several human CYP isoforms AML showed a strong competitive inhibition of CYP1A1 with a K_i value of 0.13 µM, and a moderate inhibition of CYP2B6 with a K_i of 1.95 µM. The steady-

state human plasma C_{max} of AML following 10 mg once daily doses was around 0.062 µM, corresponding to I/K_i values of 0.5 and 0.03 for CYP1A1 and CYP2B6, respectively. These I/K_i values suggest a moderate to low potential of AML to inhibit CYP1A1- and/or CYP2B6-mediated metabolic clearance. The pharmacokinetics of AML was not changed by grapefruit juice, which inhibits CYP3A4 and MDR1 in the gut, or by the CYP3A substrate sildenafil. Cimetidine, telmisartan and benazepril did not significantly alter the pharmacokinetics of AML. The potent CYP3A inhibitor dilthiazem caused an increase in plasma C_{max} and AUC of AML by up to 57% and the combined HIV protease inhibitors indinavir and ritonavir, strong inhibitors of CYP3A, increased the AUC of AML by 90%. AML did not affect the pharmacokinetics of the cardiovascular drugs digoxin but increased the AUC and C_{max} of the hypocholesteremic drug simvastatin by 28% and 43%, respectively, though without an effect on cholesterol. It caused a minor increase of cyclosporine A plasma levels.

Valsartan: Valsartan was mainly cleared through biliary excretion, and the contribution of metabolism was minor. Cytochrome P450 (CYP) 2C9 is the main enzyme responsible for the formation of the 4-hydroxyvaleryl metabolite of valsartan in human liver microsomes, a minor metabolite identified also in human faeces (9% of oral dose). Although CYP 2C9 is involved in valsartan metabolism, CYP-mediated drug–drug interaction between valsartan and other co-administered drugs could be considered negligible. Valsartan did not inhibit CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 to any significant extent. It marginally inhibited CYP2C9 with a K_i value of 135 µmol/L. The main elimination mechanism for valsartan in humans is likely to be hepatic canalicular transport by MRP2 and the currently available literature indicates that no clinically significant drug interactions occur via MRP2. However, the knowledge on substrate specificities, regulation mechanisms, and inhibitors and inducers of MRP2 is still limited. Overall, based on the preclinical and clinical findings with valsartan, the potential for clinical drug interactions on the level of drug transporters with valsartan appears to be very unlikely.

Hydrochlorothiazide: No relevant pharmacokinetic interactions have been reported between HCT and other drugs and, particularly, no drug interactions of HCT via CYP450 enzymes have been observed. In cardiovascular combination therapy, no significant pharmacokinetic interactions have been reported between angiotensin receptor blockers, calcium antagonists and thiazide diuretics. Cholestyramine and colestipol decreased absorption of HCT, which is consistent with the acidic nature of HCT.

Valsartan/amlodipine/hydrochlorothiazide: In the toxicokinetic studies following 2- and 13-week daily treatment with the combination drug AML/VAL/HCT (see section Toxicology), there was essentially no pharmacokinetic interaction between the individual components of VAL, HCT and AML. The clinical study results in humans indicated that no clinically relevant pharmacokinetic interaction exists when the drugs are administered as triple combination *vs* the corresponding dual combinations. The results are consistent with the lack of drug interaction when administered as dual combination (valsartan and hydrochlorothiazide; valsartan and amlodipine) *vs* the corresponding mono-components.

In summary, the pharmacokinetic interactions were sufficiently described for the individual compounds. Furthermore, no clinically relevant pharmacokinetic interactions were identified during the clinical trials.

Toxicology

- Single dose toxicity

No single dose toxicity studies have been conducted with AML/VAL/HCT. The lack of single dose toxicity studies is acceptable and in accordance to the current guidelines.

- Repeat dose toxicity (with toxicokinetics)

Based on the doses of VAL, HCT and AML in the clinical trials conducted with this combination, a ratio of 32:5:2 (VAL: HCT: AML) was used in the preclinical toxicology studies. The highest ratio in the clinical studies is 64:5:2 (VAL:HCT:AML). Justification of this approach was provided and was based on the assumption that this ratio had the greatest potential to demonstrate any interactions resulting in pharmacodynamic and pharmacokinetic effects to the proposed clinical use. However, it is

reasonable to assume that the use of a higher ratio of VAL in the pivotal toxicity study would only lead to a higher incidence of valsartan-related effects possibly masking the effects of the other active ingredients in the triple combination. Thus, further discussion is not needed.

Oral repeat-dose toxicity studies of the combination were conducted in rats (IGS Wistar Hannover). All animals were dosed orally by a gavage. Samples were also obtained for the toxicokinetic analysis. Two shorter dose range-finding studies (0670713, 0670714) and a pivotal 13-week study (0670715) were conducted and this in line with the CHMP guideline CHMP/SWP/258498/2005. The characteristics and the major findings are summarised in the table below.

Study ID	**Species/gender Number/Group**	**Dose/Route** (VAL/HCT/AML)	**Duration**	**NOEL/ NOAEL (mg/kg/day)**	**Major findings**
0670713 Non-GLP	Wistar rats/ 2-3/gender	Comb: Dose escalation: 64:10:4 mg/kg (day 1), 128:20:8 mg/kg (day 5) and 384:60:24 mg/kg (days 7 and 8) PO **or** 384:60:24 mg/kg/day for four days PO	Dose escalation Or Four days repeated dosing	NA	**Dose escalation:** No treatment-related findings **384:60:24 mg/kg/day:** 2/3♀ deaths (piloerection and stains was observed in one animal prior to death) Clinical: Body weight loss (♀),↓ body weight gain (♂) Microscopic pathology: slight tubular basophilia in the kidney (1/3♂), lymphoid depletion in the spleen (♀)
0670714 Non-GLP	Wistar rats/ 5/gender/group TK: 1/time point/ gender/group	Comb: 64:10:4, 128:20:8 mg/kg/day **or** 256:40:16 mg/kg/day PO	2-week dose range-finding	64:10:4	**≥ 64:10:4 mg/kg/day:** Clinical: ↓ mean body weight gain (♂),↓ average food consumption Haematology: ↓ absolute reticulocytes count **≥ 128:20:8 mg/kg/day:** Clinical: Body weight loss (♀) Haematology: A trend towards ↓ red cell mass (RBC count, [haemoglobin], haematocrit) Clinical chemistry: ↑ [serum urea] Organ weights: ↓ spleen (♂, correlated with ↓ haematopoiesis), ↓ thymus (♀) Microscopic: ↓ haematopoiesis in the spleen **256:40:16 mg/kg/day:** Mortality/unscheduled sacrifice of all animals Clinical: Rhinorrhoea, dehydration, hunched posture, reduced faeces, reddened skin, salivation Haematology: A trend towards ↓ lymphocyte counts and a slight ↑ neutrophil counts Clinical chemistry: ↑ [creatinine], ↑ [K^+], ↑ [phosphorus], ↓ [alkaline phosphatase activity] (♀) Macroscopic: red foci in the glandular stomach (3/10, correlated with erosions in 2/3 animals) Microscopic: lymphoid depletion
0670715 GLP	Wistar rats/ 10/gender/group Recovery (control and high comb): 6/gender/group TK: 10/gender/group	Comb: 8:1.25:0.5, 32:5:2 or 64:10:4 mg/kg/day PO **or** Valsartan 64 mg/kg/day PO HCT 10 mg/kg/day PO Amlodipine 4 mg/kg/day PO	13-week with a 4-week recovery period	8:1.25:0.5	**≥ 8:1.25:0.5 mg/kg/day comb:** Clinical: dose-dependent ↓mean absolute body weight gain (depending on dose up to 46% and 55% for ♂ and ♀, respectively), ↓mean body weights (up to 10%), dose-dependent ↓mean food consumption (up to 16%) Organ weight: ↓ heart weight **≥ 32:5:2 mg/kg/day comb:** 1♂ death (urinary tract obstruction, considered unrelated to treatment) Haematology: minimal ↓ red cell mass Clinical chemistry: dose-dependent ↑ [serum urea] Microscopic: Hyperplasia of the JGA in the kidney, focal erosions of the glandular stomach (♂) **64 mg/kg/day valsartan:** Clinical: ↓ mean absolute body weight gain (♀, <27%) Haematology: minimal ↓ red cell mass (♀) Organ weight: ↓ heart weight Microscopic: Hyperplasia of the JGA in the kidney, focal erosions of the glandular stomach (♂) **10 mg/kg/day HCT:** Clinical: ↓ mean absolute body weight gain (♀, <18%) **4 mg/kg/day amlopidine:** No treatment-related findings

JGA – Juxtaglomerular apparatus

The oral administration of AML/VAL/HCT for at least 2 weeks in rats (0670714) was not tolerated at 256:40:16 mg/kg/day. At 64:10:4 mg/kg/day, all animals were modestly underweight compared to concurrent controls (not statistically significant), exhibited reductions in body weight gains (statistically significant) and food consumption, and there was a mild to moderate reduction in absolute reticulocyte counts. The NOAEL was determined to be 64:10:4 mg/kg/day.

The oral administration of the triple combination of VAL/HCT/AML to rats at doses up to 64:10:4 mg/kg/day for at least 13 weeks in the pivotal rat repeated dose toxicity study (0670715) was tolerated with expected effects that were mainly associated with the VAL component of the formulation. Amongst the principal findings were:

- Moderate reductions in mean body weight and mean food consumption. The former was observed following administration of HCT alone, VAL alone and VAL/HCT/AML.
- Decrease in erythrocyte parameters. These are exaggerated pharmacological effects of VAL due to its antagonistic effect on angiotensin II.
- Increased serum urea and creatinine were considered related to an exaggerated effect of VAL due to decreased renal perfusion and subsequent ischemia following prolonged hypotensive effect.
- Focal erosions of the glandular stomach, which probably resulted from local irritation and exaggerated blood pressure reduction in ischemia and hypofusion of the stomach due to treatment.
- Decreased heart weight was seen as a response to the hypotensive action of VAL/HCT/AML, but was probably due to VAL.
- Juxtaglomerular apparatus hyperplasia in the kidney was seen as a pharmacological response to the VAL due to an increase in renin production.

Exposures to VAL, HCT and AML respectively to NOAEL in rat toxicity studies were up to 1.95, 10.45 and 2.16 times higher than those at the highest dose in human (320/25/10 mg, VAL/HCT/AML, respectively), suggesting a moderate safety margin for human. While NOAEL was not definitely established, it was considered to be 8:1.25:0.5 mg/kg/day.

The exposure to AML and HCT was proportional to the dose. The exposure data of VAL are difficult to interpret in relation to dose proportionality. AML seemed to accumulate upon repeated dosing, but this was not the case for VAL and HCT. Gender-differences were apparent for AML as the exposure in females had a tendency to be higher than that in males. Co-administration had no impact on the toxicokinetics of HCT and AML, while an effect on the toxicokinetics of VAL cannot be excluded completely as the exposure to VAL seemed to be higher in the combination as compared to VAL administrated alone. It is not possible to assess whether the higher exposure of VAL observed in the pivotal toxicity study led to an increased toxicity at lower dosages as VAL alone was only tested at the highest dose. Clinical data have sufficiently shown lack of differences on pharmacokinetics when the compounds are administrated in dual and triple combination as compared to when administrated alone. All effects could be ascribed to the pharmacological effects of the product and seemed reversible or partially reversible following termination of the treatment. Thus, the CHMP concluded that there were no major unexpected interactions with the combination within an adequate range of concentrations and exposures in rat given VAL/HCT/AML as a combination product or separately for up to 13 weeks. No additional non-clinical pharmacokinetic studies are requested. Considerations given in CHMP guideline for the development of fixed combinations (CHMP/EMEA/CHMP/SWP/258498/2005) have been taken into account.

- Genotoxicity

No genotoxicity studies were conducted with AML/VAL/HCT. There is no evidence of genotoxicity for VAL and AML from previous use. Both VAL and AML are considered to be non-genotoxic compounds. Hydrochlorothiazide, on the other hand, showed genotoxic potential in two *in vitro* tests for mutagenicity and cytogeneticity; the mouse lymphoma assay and sister chromatid exchange assay (*in vitro* cytogenetics). Although the available reviews in literature suggest that the *in vivo* mutagenic potential of HCT is considered low, the CHMP requested further information about the lack of *in vivo* genotoxicity of hydrochlorothiazide either based on published literature or experimental non clinical data. However, the response did not provide additional published scientific literature or the original study reports of the *in vivo* genotoxicity testing, which is required for sufficient full assessment in accordance with the guideline on mixed marketing. Exceptionally, the lack of this information is

deemed acceptable because of a) the reviewed *in vitro* and *in vivo* genotoxicity studies indicated that HCT is unlikely to be genotoxic, b) the lack of carcinogenicity findings in non clinical studies, and c) the extensive clinical use of HCT in patient for over fifty years.

- Carcinogenicity

No carcinogenicity studies were conducted with the triple combination of AML/VAL/HCT. The carcinogenicity of the three compounds was considered separately. This is acceptable in accordance to the current guideline on fixed combinations as none of the compound is considered carcinogenic.

- Reproduction Toxicity

No reproductive and developmental toxicity studies were conducted with the triple combination of AML/VAL/HCT. AML is contraindicated in first trimester and VAL in first, second and third trimester. The non clinical studies with AML/VAL/HCT are unlikely to reveal significant information.

Toxicity to reproduction has earlier been assessed for AML and VAL, separately. There was no evidence of VAL teratogenicity, but there was evidence of foetotoxicity of VAL in the Segment II rabbit study and a reduction in pup development and survival in the Segment III rat study. There was no evidence of AML teratogenicity; here were no effects on the reproductive performance of rats in segment I study. However, AML decreased the litter size, increased intrauterine deaths and prolonged the gestation period and duration of labour. In addition, the embryo-foetal development of the dual combination of VAL and AML has also been investigated. While the use of AML/VAL during pregnancy is not recommended during the first trimester and is contraindicated for the two latter trimesters, the use of HCT may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia and may be associated with other adverse reactions, as stated in the SPC. No juvenile animal studies were conducted with the triple combination of AML/VAL/HCT, which is not recommended for use in patients below age 18 years due to a lack of data on safety and efficacy. The lack of juvenile animal studies is acceptable.

- Local tolerance

No local tolerance studies were conducted with the triple combination of AML/VAL/HCT. The lack of local tolerance studies is acceptable due to the clinical experience and the route of administration, *per os*.

- Other toxicity studies

Studies on impurities

The lack of toxicology studies on impurities was explained by the fact that the evaluated impurities were within specified limits. The CHMP requested a further elaboration on the impurity levels of AML/VAL/HCT in accordance with the current ICH guidelines and the CHMP guideline on limits of genotoxic impurities (CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006). In response, the details of the impurity levels were adequately provided and lack of safety testing justified.

Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) report was submitted with a phase 2 environmental risk assessment performed for all three active pharmaceutical ingredients. VAL shows moderate chronic toxicity to aquatic species; the reproduction rate in Daphnia magna being specially affected. It has no significant potential to inhibit the microbial activity of activated sludge, and is not readily biodegradable. The substance is not expected to bio-accumulate. Adsorption to sludge was low and retention in sewage sludge during the passage of sewage treatment plants is unlikely. The study on the transformation of VAL in aerobic water-sediment systems showed some partitioning of VAL into sediment, however, after 7 days only between 11.7 and 12.4 % of the substance were found as parent compound in sediment. Degradation occurs *via* the formation of a major metabolite 2'-(1H-tetrazol-5-yl)-biphenyl-4-carboxylic acid and other minor metabolites. AML shows significant chronic toxicity to aquatic species and has potential to inhibit the microbial activity of activated sludge at high concentrations. It is not readily biodegradable and based on its physical-chemical properties and its high susceptibility to oxidative metabolism in higher organisms it is not expected to bio-accumulate.

AML was found to be photolabile. The compound shows moderate adsorption to sludge and partitioning into sediments with only 5.3 to 6.0 % of applied radioactivity as parent substance found in sediments after 21 days. HCT shows low chronic toxicity to aquatic organisms, has no significant potential to inhibit the microbial activity of activated sludge and is not readily biodegradable. It is neither expected to adsorb to a significant extend to soil, sludge or sediments nor anticipated to bio-accumulate, as judged from its low log P.

Overall, the Phase II – Tier A assessment for AML, VAL and HCT does not indicate any significant concerns for surface water, sewage treatment plants, sediment compartments and groundwater. Nevertheless, the CHMP expressed a serious concern that the methods used for determination of the log K_{ow} for the three compounds and the study reports for the Ready Biodegradability Test for HCT and AML were not submitted. Only official safety data sheets for amlodipine besylate and HCT were provided. In addition, the Algae Growth Inhibition Test (OECD 201) for VAL was not valid as both, the water and the solvent control exceeded the coefficient of variation of average specific growth rates. Due to the fact that full results of the evaluation were not presented as study reports, the CHMP requested the detailed information on all performed test with all three substances in order to fully evaluate the ERA for AML/VAL/HCT. In response, a commitment to conduct below stated environmental assessment evaluation studies has been given. Considering the extensive clinical use of AML, VAL and HCT individually and also in dual combinations, these follow-up measures is deemed acceptable. For AML following studies will be conducted and results to be provided together with updated ERA:

- Algae growth inhibition (OECD201)
- An additional study to confirm the octanol/water partition coefficient as study protocol for the log Kow value is not available
- Fish early life-stage study (OECD210)

For VAL following studies will be conducted and results to be provided together with updated:

- Algae growth inhibition (OECD201)
- Activated sludge respiration inhibition (OECD209)
- An additional study to confirm the octanol/water partition coefficient as a study protocol for the logKow value is not available
- Toxicity to sediment-dwelling organisms.

For the active ingredient HCT all the remaining studies required for a full Phase II-Tier A assessment will be delivered together with an updated ERA, i.e. octanol-water partition coefficient, algae growth inhibition, ready biodegradability, adsorption-desorption properties and transformation in water-sediment systems.

2.4 Clinical aspects

Introduction

This is an application for a fixed combination product containing amlodipine, valsartan and hydrochlorothiazide in the frame of the centralised procedure submitted in accordance with Article 3(2)(a) of the Regulation (EC) no. 726/2004 and with Article 10b of Directive 2001/83/EC, as amended (fixed combination products). A full dossier has been submitted.

The objective of the clinical program was to demonstrate the efficacy and safety of the combination of valsartan, hydrochlorothiazide and amlodipine in the treatment of essential hypertension. The lower strengths (VAL/HCT/AML 160/12.5/5 mg, 160/12.5/10 mg, 160/25/5 mg, 160/25/10 mg), which are widely used in clinical practice as mono- or dual therapies, are supported by biopharmaceutical data. The highest dose, containing 320/25/10 mg VAL/HCT/AML, has been studied in a short term phase III parallel group trial comparing three dual combinations. Thus, the development programme consists of:

1. Phase III clinical study to demonstrate the efficacy and safety of the triple combination;
2. Biopharmaceutical development program to demonstrate bioequivalence between the fixed triple combination of final market image (FMI) tablet and the free combination of corresponding doses of the clinical service formulations (CSFs) in the phase III clinical study;

3. Pharmacokinetic interaction study;
4. Bioequivalence study to address the sourcing of amlodipine;
5. Food effect bioavailability study with the FMI tablet.

The triple fixed combination tablet is intended to replace the free combination of three individual component drugs; or the combination of dual VAL/HCT + AML; or the combination of dual AML/VAL + HCT.

The claimed indication is:
Treatment of essential hypertension.
Exforge HCT is indicated as replacement therapy in patients whose blood pressure is adequately controlled on amlodipine, valsartan and hydrochlorothiazide (HCT) used as individual or combination therapies.

The approved indication is:
Treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual-component and a single-component formulation.

The regulatory requirements relevant for fixed dose antihypertensive drug combinations are described in the following regulatory guidance documents:

1. Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, CPMP/EWP/238/95 Rev. 3.
2. Guideline on clinical development of fixed combination medicinal products, CPMP/EWP/240/95 Rev.1.
3. 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, CHMP/EWP/191583/05.
4. Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1).
5. Questions & Answers on the Bioavailability and Bioequivalence Guideline (CHMP/EWP/40326/06).

The design and conduct of the clinical studies followed the relevant regulatory authority guidelines in effect at the time of study initiation. Scientific Advice regarding the clinical development program for amlodipine/valsartan/hydrochlorothiazide medicinal product and study design was sought from the CHMP in July and August 2007 (SAWP/308650/2007 and EMEA/H/SA/908/1/2007/II) and national regulatory authorities. The CHMP advice related to the requirements for development of the combination product with replacement indication. In principle, the CHMP agreed that formal bioequivalence studies would suffice, but pointed out that additional efficacy/safety data would be needed for 320 mg dose of valsartan prior to acceptance of the triple combination with this higher dose. Several critical issues were raised regarding the design of the pivotal study VEA2302. The CHMP Scientific advice has been followed in part, but as the clinical studies were on-going at the time of advice, the recommendations on the design of the pivotal study were not implemented. The national regulatory authorities' advice was sought mainly for the 'second line' indication (France, the Netherlands, Sweden, and the United Kingdom, 2004).

Exforge HCT was granted a product specific waiver and there is no paediatric development programme or paediatric studies.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. The assessment of the clinical data did not raise concerns about their compliance with GCP. No inspection was requested.

Pharmacokinetics

Since the tolerability of the three drug components of the fixed dose combination product are well known as monotherapies or dual combination, no initial tolerability studies were conducted in healthy subjects. The bioequivalence development programme was designed to bridge the information obtained in definitive clinical efficacy and safety study (VEA489A2302) with the free combination of the CSFs to the fixed combination tablet products. Two bioavailability studies were conducted with the dose strengths of 10/160/25mg (VEA489A2306) and 5/160/12.5mg (VEA489A2305) of AML/VAL/HCT. Furthermore, based on the compositional proportionality or similarity of active/inactive ingredients, and similarity in *in vitro* dissolution properties, bio-waivers were requested for the other three dose strengths, 10/160/12.5mg, 5/160/25mg and 10/320/25mg of AML/VAL/HCT. Since AML CSF used in the phase III study was an over-encapsulated product that utilised an AML tablet (Norvasc®) obtained from the US market, two additional bioequivalence studies were conducted. One study addressed the bioequivalence between the AML CSF and US sourced AML (VEA489A2105) and the other study addressed the bioequivalence between the FMI tablet and the EU sourced AML (VEA489A2106). In summary, the biopharmaceutics and pharmacokinetics development program consisted of the following studies:

Study A2104 - *A multi-center, multiple dose, open-label, four-cohort, parallel study to assess the pharmacokinetic drug interaction following co-administration of valsartan, hydrochlorothiazide and amlodipine in patients with hypertension.*

Study A2310 - *A randomized, open-label, single-dose, two-period crossover study in healthy subject to evaluate the effect of food on the bioavailability of valsartan/hydrochlorothiazide/amlodipine 320 mg/25 mg/10 mg fixed combination final market image tablet.*

Study A2305 - *An open-label, randomized, single dose, four period, crossover study to determine the relative bioavailability of three prototype 160 mg/12.5 mg/5 mg fixed combination valsartan/hydrochlorothiazide/amlodipine tablets to a free combination of phase III-clinical service forms of 160 mg valsartan, 12.5 mg hydrochlorothiazide, and 5 mg amlodipine.*

Study A2306 - *An open-label, randomized, single dose, three period, crossover study to determine the relative bioavailability of two prototype 160 mg/25 mg/10 mg fixed combination valsartan/hydrochlorothiazide/amlodipine tablets to a free combination of phase III-clinical service forms of 160 mg valsartan, 25 mg hydrochlorothiazide, and 10 mg amlodipine.*

Study A2106 - *An open label, randomized, single-dose, two-way crossover study to determine the bioequivalence of the amlodipine component between the fixed combination of 160 mg/25 mg/10 mg valsartan/hydrochlorothiazide/amlodipine final market image tablet and the 10 mg amlodipine tablet (Istin®) administered in combination with 160 mg valsartan and 25 mg hydrochlorothiazide tablets.*

Study A2105 - *An open label, randomized, single-dose, two-way crossover study to determine the bioavailability of 5 mg amlodipine clinical service form capsule relative to that of the 5 mg amlodipine administered as one 5 mg Norvasc® tablet.*

During the procedure, as response to the CHMP concern, the following study report has been submitted:
CSPH100A2105 - *An open-label, single-dose, three-period, crossover study to assess the bioequivalence of hydrochlorothiazide (HCTZ) following administration of 25 mg dose between Clinical Service Form (CSF) capsule and European marketed tablet or Canadian-marketed tablet Formulations in healthy subjects*

- Absorption, distribution, elimination

The pharmacokinetics of VAL, HCT and AML have been well characterised when administered alone or when administered as the double combinations (VAL/HCT or VAL/AML). Following oral

administration of the fixed combination of VAL/HCT/AML under fasted conditions, peak plasma concentrations of VAL, HCT and AML are reached in 3-4, 1-3 and 6-9 hours, respectively. The elimination half lives of VAL, HCT and AML are about 13-23, 10-12, 41-47 hours, respectively. The rate and extent of absorption of the fixed combination of VAL/HCT/AML are equivalent to the bioavailability of VAL, HCT and AML when administered as individual tablets.

Bioequivalence and Bioavailability

No specific studies have been conducted to characterise the absolute and relative bioavailability of three drug components after the administration of the triple combination tablet because the triple combination product is intended for the replacement of individual drug products. However, in the pivotal clinical trials the components were administered as clinical service formulations (CSFs) and in order to bridge the data obtained in these pivotal studies with the fixed combination product, a bioequivalence development programme was conducted. Five clinical studies were conducted to examine the bioavailability and bioequivalence of VAL, AML and HCT and the effect of food on their bioavailability. Details of these biopharmaceutical studies are summarized below:

Summary of biopharmaceutics studies

Study No.	Objective	Population		Dosage form	Dose	N
VEA489A2305	Bioavailability	HS	M/F	Valsartan (CSF)	160 mg SD	32
				HCTZ (CSF)	12.5 mg SD	
				Amlodipine (CSF)	5 mg SD	
				Amlodipine/Valsartan/HCTZ (FMI)	5/160/12.5 mg SD	
VEA489A2306	Bioavailability	HS	M/F	Valsartan (CSF)	160 mg SD	30
				HCTZ (CSF)	25 mg SD	
				Amlodipine (CSF)	10 mg SD	
				Amlodipine/Valsartan/HCTZ (FMI)	10/160/25 mg SD	
VEA489A2105	Bioequivalence	HS	M/F	Amlodipine (CSF)	5 mg SD	24
				Amlodipine (US Sourced)	5 mg SD	
VEA489A2106	Bioequivalence	HS	M/F	Amlodipine/valsartan/HCTZ (CSF)	10/160/25 mg SD	26
				Valsartan (CSF)	160 mg SD	
				HCTZ (CSF)	25 mg SD	
				Amlodipine (EU sourced)	10 mg SD	
VEA489A2310	Food-Effect	HS	M/F	Amlodipine/valsartan/HCTZ (FMI)	10/320/25 mg SD	32

HS: Healthy subjects, M = Male, F = Female; CSF = Clinical service form, FMI = Final market image; SD: single dose

Study VEA489A2305 and study VEA489A2306

Study VEA489A2305 was an open-label, single dose, four-period, crossover bioavailability study conducted in order to determine the relative bioavailability of three different prototypes fixed combination tablet containing 5 mg AML, 160 mg VAL and 12.5 mg HCT compared to the corresponding doses of free combination of clinical service formulations (CSFs), which were used in the pivotal efficacy and safety trial. Study VEA489A2306 was an open-label, single dose, three-period, crossover bioavailability study conducted in order to determine the relative bioavailability of two different prototype fixed combination tablets containing 10 mg AML, 160 mg VAL and 25 mg HCT compared to the corresponding doses of free combination of CSFs used in the pivotal efficacy and safety trial. The comparative bioavailability assessments in both studies were performed based on the 90% CI for the estimated ratio of geometric means of AUC and C_{max} of each drug. The results of the statistical evaluation are provided in the table below.

Statistical summary of relative bioavailability of 5/160/12.5 mg amlodipine/valsartan/HCTZ fixed combination tablets compared to the free combination of CSFs (Study CVEA489A2305)

		Ratio of geometric means (90% CI)		
Analyte	PK parameter	VEA489A Prototype I	VEA489A Prototype II	VEA489A Prototype III
Valsartan	$AUC_{(0-t)}$	1.02 (0.88-1.19)	1.13 (0.97-1.32)	1.10 (0.95-1.28)
	$AUC_{(0-inf)}$	1.04 (0.90-1.20)	1.15 (0.99-1.33)	1.19 (1.03-1.39)
	Cmax	1.00 (0.84-1.20)	1.17 (0.97-1.40)	0.99 (0.83-1.18)
HCTZ	$AUC_{(0-t)}$	0.99 (0.94-1.04)	1.06 (1.00-1.11)	1.00 (0.95-1.05)
	$AUC_{(0-inf)}$	0.99 (0.95-1.04)	1.05 (1.00-1.10)	1.00 (0.95-1.05)
	Cmax	1.00 (0.91-1.10)	1.08 (0.99-1.19)	0.99 (0.90-1.09)
Amlodipine	$AUC_{(0-t)}$	1.00 (0.94-1.07)	0.97 (0.90-1.04)	1.05 (0.98-1.13)
	$AUC_{(0-inf)}$	1.01 (0.94-1.08)	0.97 (0.91-1.04)	1.05 (0.98-1.13)
	Cmax	1.03 (0.96-1.11)	0.99 (0.92-1.07)	1.06 (0.98-1.14)

CI: confidence interval

Statistical summary of relative bioavailability of 10/160/25 mg amlodipine/valsartan/HCTZ fixed combination tablets compared to the free combination of CSFs (Study CVEA489A2306)

		Ratio of geometric means (90% CI)	
Analyte	PK parameter	VEA489A Prototype I	VEA489A Prototype II
Valsartan	$AUC_{(0-t)}$	0.96 (0.86, 1.06)	1.05 (0.94, 1.16)
	$AUC_{(0-\infty)}$	0.99 (0.89, 1.10)	1.07 (0.96, 1.19)
	C_{max}	0.97 (0.85, 1.11)	1.03 (0.91, 1.17)
HCTZ	$AUC_{(0-t)}$	1.01 (0.96, 1.06)	1.04 (0.99, 1.09)
	$AUC_{(0-\infty)}$	1.00 (0.96, 1.05)	1.03 (0.98, 1.08)
	C_{max}	0.97 (0.89, 1.06)	1.01 (0.93, 1.10)
Amlodipine	$AUC_{(0-t)}$	1.02 (0.94, 1.11)	1.06 (0.97, 1.15)
	$AUC_{(0-\infty)}$	1.02 (0.93, 1.11)	1.05 (0.97, 1.14)
	C_{max}	1.02 (0.94, 1.11)	1.04 (0.96, 1.13)

The pharmacokinetic and statistical results indicated that in study VEA489A2305 the 90% CI for the ratios of geometric means for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for VAL, HCT and AML for the prototype I formulation were within the required bioequivalence range of 0.8-1.25, which indicates that the rate and extent of absorption for VAL, HCT and AML from prototype I tablets were similar to those of the free combination treatment. Prototype I of 5 mg/160 mg/12.5 mg fixed combination tablets met the bioequivalence criteria for comparison to the free combination of CSFs of 5 mg AML, 160 mg VAL and 12.5 mg HCT. However, based on the pharmacokinetic and statistical results in the second study, VEA489A2306, both, the prototype I and prototype II formulations, were within the required bioequivalence range of 0.8-1.25, which indicates that the rate and extent of absorption for VAL, HCT and AML from these two tablets were similar to those of the free combination treatment. This contrasts with the study VEA489A2305, where only the prototype I of 5 mg/160 mg/12.5 mg fixed combination tablets met the required bioequivalence criteria with the free combination of CSFs of 5 mg AML, 160 mg VAL and 12.5 mg HCT. It was convincingly argued that the differences in bioequivalence between the two strengths of fixed combinations as compared to the prototypes I and II can be ascribed to differences in the total coefficients of variations for C_{max} and AUC resulting in higher intra-subject variability for 5 mg tablet. Based on the results from VEA489A2306 study, the 10 mg/160 mg/25 mg prototype I tablet was selected and used in *in vitro* studies to support bio-waiver requests for 5/160/25 mg and 10 mg/160 mg/12.5 mg AML/VAL/HCT tablets.

Study VEA489A2105 and study VEA489A2106

Two additional bioequivalence studies were conducted, since the AML CSF used in the phase III study was an over-encapsulated product that utilised an AML tablet (Norvasc) obtained from the US market. One study addressed the bioequivalence between the AML CSF and US sourced AML product (Study VEAA2105) and the other study addressed the bioequivalence between the FMI tablet and the EU sourced AML product (Study VEAA2106).

Study VEA489A2105 was an open-label, randomized, single-dose, two-way crossover study to determine the bioavailability of 5 mg AML CSF capsule relative to that of the 5 mg AML Norvasc tablet. The rate and extent of absorption of AML were equivalent between 5 mg AML CSF capsule and the 5 mg AML US marketed tablet, as the 90% confidence intervals for AML AUC and C_{max} were both within the bioequivalence limit (0.80-1.25). Thus, bioequivalence has been demonstrated between the two formulations of AML. Study VEA489A2106 was conducted to examine bioequivalence between the 10/160/25 mg AML/VAL/HCT FMI tablet and EU-registered 10 mg AML reference product Istin when given in free combination with 160 mg VAL and 25 mg HCT CSF. The AML component of AML/VAL/HCT FMI fixed combination tablet was fund to be bioequivalent with the 10 mg AML tablet Istin. Nevertheless, during the evaluation process the CHMP raised a major objection, since results of studies to prove bioequivalence with a product registered in Europe were provided only for AML and not for HCT and VAL. The pivotal studies proving efficacy of the combination product were conducted with the individual in-house formulations and according to the *Note for Guidance on the investigation of bioavailability and bioequivalence* (CPMP/EWP/QWP/1401/98), the bioequivalence should be proven to show bioequivalence with EU source reference products for VAL and HCT. In response, it was stated that the core composition and method of manufacture of VAL CSF and VAL in Diovan are identical. Thus, the only difference in the two products relates to the pigment in the film coating as given in the table above. As regards HCT, a bioequivalence study confirming bioequivalence in terms of both AUC and C_{max} between HCT CSF and HCT from the EU marketed product was conducted and submitted during the procedure. The major objections were thus resolved.

Bio-waiver for 5 mg/160 mg/25 mg and 10 mg/160 mg/12.5 mg AML/VAL/HCT
The manufacturing process and the qualitative composition of 5/160/25 mg and 10/160/12.5 mg AML/VAL/HCT formulations is identical to that of the Prototype I of 10 mg/160 mg/25 mg fixed combination tablet, for which the bioequivalence was established in the earlier studies. The quantitative compositions are also similar. The total difference of microcrystalline cellulose between the 5 mg and 10 mg formulations for 5 mg/160 mg/25 mg AML/VAL/HCT and between the 12.5 mg and 25 mg formulations for 10 mg/160 mg/12.5 mg AML/VAL/HCT would have no impact on the performance of the product. Dissolution of FMI tablets was tested under various pH values. The mean cumulative % released *vs* time profiles of the 5 mg/160 mg/25 mg and 10 mg/160 mg/25 mg tablets and between the 10 mg/160 mg/12.5 mg and 10 mg/160 mg/25 mg tablets were similar for VAL, HCT and AML at three pH values. Considering the composition similarity and the same manufacturing process; the pharmacokinetic characteristics of VAL, HCT and AML; and the acceptable *in vitro* dissolution results, the requirements for waiver for a bioequivalence study with 5 mg/160 mg/25 mg and with 10 mg/160 mg/12.5 mg AML/VAL/HCT are fulfilled.

Bio-waiver for 10/320/25 mg AML/VAL/HCT
The request for bio-waiver for the 10 mg/320 mg/25 mg AML/VAL/HCT fixed combination FMI tablet is proposed based on the following points: the manufacturing process of 10 mg/320 mg/25 mg AML/VAL/HCT fixed combination FMI tablet is identical to that of the 5/160/12.5 mg fixed combination prototype I tablet, for which the bioequivalence was established; the composition of 10 mg/320 mg/25 mg AML/VAL/HCT fixed combination FMI tablet is proportional in its active and inactive ingredients to the 5 mg/160 mg/12.5 mg AML/VAL/HCT fixed combination prototype I tablet; VAL, HCT and AML exhibit linear and dose proportional pharmacokinetics. Considering the above mentioned arguments, the request for bio-waiver was deemed acceptable.

Effect of food
The effect of food on the bioavailability of AML/VAL/HCT 10 mg/320 mg/25 mg fixed combination FMI tablet was evaluated in a randomised, open-label, single-dose, two-period crossover study CVEA489A2310 in healthy subjects. Subjects were randomized to one of the two treatment sequences, with 18 subjects in each of the two sequences and received a single 320 mg/25 mg/10 mg oral dose of AML/VAL/HCT FMI tablet under fasted or fed conditions. Subjects who were dosed in the fed state consumed a standard FDA high fat breakfast. Each treatment period was separated by at least 14 days. The results showed that C_{max} of VAL increased by 12% and AUC_{0-t} and $AUC_{0-\infty}$ increased by 14% in the presence of food as compared to the fasted condition. The upper limit of 90%

CI for both C_{max} and AUC was between 1.25 and 1.32. The magnitude of the increase in both C_{max} and AUC is less than the total variability (~30.9 – 44.2%) observed in this study and hence, it is not expected to be clinically relevant. The bioavailability of VAL, HCT and AML is similar under fed and fasting conditions following a single dose oral administration of 10 mg/320 mg/25 mg AML/VAL/HCT fixed combination tablet.

- Dose proportionality and time dependencies

No specific pharmacokinetic studies were conducted.

- Special populations

There were no specific pharmacokinetic studies conducted in special populations. Population PK analysis was conducted in the phase III safety and efficacy study in hypertension patients to assess the potential of pharmacokinetic drug-drug interaction (VEA489A2302). Results indicated that the pre-dose concentrations of VAL, HCT, and AML in steady state were comparable between the triple combination and the corresponding dual combination treatments.

- Pharmacokinetic interaction studies

Pharmacokinetic interaction studies focused on the investigation of the possible interactions between VAL, AML and HCT. The pharmacokinetics of VAL, HTC and AML following administration of the triple combination was investigated in two clinical studies in patients with hypertension.

Study VEA489A2104

Study VEA489A2104 was a multi-centre, multiple dose, open label, four-cohort, parallel study conducted in order to assess the pharmacokinetic drug-drug interaction following co-administration of VAL, HCT and AML in patients with hypertension. Doses used in the study represented the highest doses approved for VAL/HCT and VAL/AML double combinations and the highest proposed doses of the triple combination. The doses and the design used in this study were similar to those used in the pivotal efficacy and safety phase III study VEA489A2302 (see section *Clinical efficacy*). A total of 120 male and female patients were planned to be enrolled in the study and 101 patients completed the study. The statistical overview of the effects of VAL on the pharmacokinetics of HCT and AML are given in table below.

Summary of statistical results for valsartan effect on day 17 pharmacokinetics of hydrochlorothiazide and amlodipine

Analyte	Parameter	Adjusted geometric mean		Ratio of geometric means (90% CI)
		V/H/A (test) N = 23	H/A (reference) N = 23	
HCTZ	$AUC_{0-\tau,ss}$ (ng.h/mL)	1868.6	1726.1	1.08 (0.89 - 1.32)
	$C_{max,ss}$ (ng/mL)	219.3	264.7	0.83 (0.69 - 0.99)
Amlodipine	$AUC_{0-\tau,ss}$ (ng.h/mL)	494.8	453.6	1.09 (0.90 - 1.32)
	$C_{max,ss}$ (ng/mL)	25.1	22.8	1.10 (0.92 - 1.32)

Addition of valsartan to HCT/AML combination increased AUC of HCT by 8% and decreased C_{max} by 17%. Addition of VAL to HCT/AML combination increased AUC and C_{max} of amlodipine by 9% and 10%, respectively. The 90% confidence intervals (CI) for geometric mean ratios for both HCT and AML exposure were not within 80 – 125% range. The observed minor changes in the exposure were not considered clinically significant and do not warrant any dosage adjustment. The statistical overview of the effects of HCT on the pharmacokinetics of VAL and AML are given in table below.

Summary of statistical results for hydrochlorothiazide effect on day 17 pharmacokinetics of valsartan and amlodipine

Analyte	Parameter	Adjusted geometric mean		Ratio of geometric means (90% CI)
		V/H/A (test) N = 23	V/A (reference) N = 23	
Valsartan	$AUC_{0-\tau,ss}$ (ng.h/mL)	73385.6	58628	1.25 (0.98 - 1.59)
	$C_{max,ss}$ (ng/mL)	9926.6	8136.3	1.22 (0.98 - 1.52)
Amlodipine	$AUC_{0-\tau,ss}$ (ng.h/mL)	494.8	451	1.10 (0.91 - 1.33)
	$C_{max,ss}$ (ng/mL)	25.1	22.8	1.10 (0.92 - 1.32)

Addition of hydrochlorothiazide to VAL/AML combination increased AUC and C_{max} of VAL by 25% and 22%, respectively; the 90% CI for geometric mean ratios for VAL exposure were not with in the 80 – 125% range. However, the observed increases in VAL exposure were less than the pharmacokinetic variability in this study and hence, were not considered clinically significant. On the other hand, addition of HCT to VAL/AML combination increased both AUC and C_{max} of AML by 10%; the 90% CI for geometric mean ratios for AML exposure was not within the 80 – 125% range. However, the observed minor changes in the exposure were not considered clinically significant and do not warrant a dosage adjustment. The statistical overview of the effects of AML on the pharmacokinetics of VAL and HCT are given in table below.

Summary of statistical results for amlodipine effect on day 17 pharmacokinetics of valsartan and hydrochlorothiazide

Analyte	Parameter	Adjusted geometric mean		Ratio of geometric means (90% CI)
		V/H/A (test) N = 23	V/H (reference) N = 25	
Valsartan	$AUC_{0-\tau,ss}$ (ng.h/mL)	73385.6	66902.5	1.10 (0.88 - 1.37)
	$C_{max,ss}$ (ng/mL)	9926.6	8595.5	1.15 (0.94 - 1.41)
HCTZ	$AUC_{0-\tau,ss}$ (ng.h/mL)	1868.6	1813.3	1.03 (0.86 - 1.24)
	$C_{max,ss}$ (ng/mL)	219.3	215.7	1.02 (0.86 - 1.20)

Addition of amlodipine to VAL/HCT combination increased VAL AUC by 10% and C_{max} by 15%; the 90% CI for geometric mean ratio of VAL exposure was not within 80-125% range. However, the observed increase in VAL exposure was minor and not considered clinically significant. On the other hand, addition of amlodipine to VAL/HCT combination increased HCT AUC by 3% and C_{max} by 2%. The 90% CI for the geometric mean ratio of HCT exposure was within 80-125% range suggesting no effect of AML on HCT exposure.

Overall, based on the results of study VEA489A2104 and considering that AML/VAL/HCT is indicated as replacement therapy in patients adequately controlled on AML, VAL and HCT, there are no observations that would give rise to considerations for dosage adjustment. Study VEA489A2104 was a parallel group study with a relatively low number of subjects enrolled per treatment arm. The pharmacokinetics of VAL was most affected when administered as part of the triple combination compared to the dual combination. Addition of HCT increased the $AUC_{0-\tau}$ of VAL by 1.25 when administered simultaneously with AML. However, no significant pharmacokinetic interaction had been reported when VAL was administered with HCT (without the presence of AML). It could be concluded that no significant pharmacokinetic interaction occurs, assuming that the safety and efficacy of the triple combination is sufficiently demonstrated in phase III efficacy studies.

Study VEA489A2302

Study VEA489A2302 was a phase III multinational, multicenter, randomized, double-blind, parallel-group trial in patients with moderate to severe hypertension. The primary objective of this study was to determine safety and efficacy of combinations of VAL, HCT and AML in patient with hypertension at the highest doses of AML/VAL/HCT (10/320/25mg) *vs* the three fixed doses of dual combinations. In addition, steady-state pre-dose plasma concentration were collected to assess the treatment compliance and to understand the potential for pharmacokinetic drug-drug interaction. The study included a single-blind run-in period of up to 4 weeks followed by an 8-week double-blind treatment period. Steady state was reached by week 5 and the plasma concentrations of VAL, HCT and AML were determined at pre dose (C_{min}) and at visits of weeks 5 and 9. The statistical comparison made

between the treatments after combining the data from weeks 5 and 9 were presented below. The concentrations of each analyte were compared between the triple combination (test) *vs* the corresponding dual combination treatments (reference).

Statistical analysis results of valsartan Cmin (PK population)

Treatment (mg)	N	Geometric mean (ng/mL)	Ratio of geometric means (90% CI)
Val/HTCZ/Aml 320/25/10 (test)	509	351.22	
Val/HTCZ 320/25 (reference)	498	337.34	1.04 (0.92, 1.18)
Val/Aml 320/10 (reference)	512	287.27	1.22 (1.08, 1.38)

Statistical analysis results of HCTZ Cmin (PK population)

Treatment (mg)	N	Geometric mean (ng/mL)	Ratio of geometric means (90% CI)
Val/HTCZ/Aml 320/25/10 (test)	509	16.14	
Val/HTCZ 320/25 (reference)	498	16.13	1.00 (0.91, 1.10)
HTCZ/Aml 25/10 (reference)	495	14.8	1.09 (0.99, 1.20)

Statistical analysis results of amlodipine Cmin (PK population)

Treatment (mg)	N	Geometric mean (ng/mL)	Ratio of geometric means (90% CI)
Val/HTCZ/Aml 320/25/10 (test)	509	10.6	
Val/Aml 320/10 (reference)	512	10.85	0.98 (0.91, 1.05)
HTCZ/Aml 25/10 (reference)	495	11.25	0.94 (0.87, 1.02)

The point estimate and the 90% CI for the ratio of geometric means for the triple combination *vs* VAL/HCT are well within the 0.8 to 1.25, suggesting that VAL concentrations at trough are comparable between these treatments. The 90% CIs between the triple and VAL/AML treatment were outside the upper limit of the 0.8 to 1.25 (1.08 to 1.38), suggesting that there was 22% increase in C_{min} with triple combination compared to VAL/AML treatment. However, this increase is within the intrinsic variability of valsartan concentration, therefore the observed differences in the C_{min} of valsartan are not considered clinically significant. All other results were acceptable.

- Pharmacokinetics using human biomaterials

There were no pharmacokinetic studies conducted with human biomaterials.

Pharmacodynamics

Valsartan is an angiotensin receptor blocker (ARB) and the blockage of AT1 receptor was confirmed by the increases of PRA and AngII after single or multiple doses treatment in healthy subjects and as well as in hypertensive subjects. The blockage of AT1 receptor up to 24 h after following a single dose of VAL at 40 and 80 mg was clearly demonstrated in healthy subjects. VAL also exerted rapid and persistent AngII inhibition effect up to 24 h post dose following multiple doses of 80 mg for 7 days. AML has been shown to be effective in reducing systolic and diastolic hypertension in patients without affecting the humoral responses such as plasma renin activity. Hydrochlorothiazide exerts its diuretic effect by reducing the re-absorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. The excretion of other electrolytes, notably potassium and magnesium, is also increased and the excretion of calcium is reduced. The antihypertensive effect of HCT is probably partly due to a reduction in peripheral resistance. Clinical pharmacology studies specifically designed to evaluate the pharmacodynamics of the fixed combination of VAL/AML/HCT were not performed. The lack of pharmacodynamic studies is acceptable as this combination product concerns three already approved drugs for the same indication and pharmacokinetic studies revealed no interactions between the three components.

Clinical efficacy

- Dose response study

No dose response studies were conducted as the proposed indication for VAL/AML/HCT fixed combination product is a substitution indication, and all proposed strengths of the three active substances are already authorised.

- Main studies

The clinical development programme for VAL/AML/HCT fixed combination consisted of ten clinical studies. Two completed studies, VEA A2302 and VEA ABR01, were designed to assess the efficacy and safety of the VAL/AML/HCT combination. VEA 2302 is the main, controlled, pivotal trial, whereas VEA ABR01 is a supportive, open-label, uncontrolled trial. There is a further study, VAA A2201E, which provides long-term efficacy and safety data in a group of patients not adequately controlled on VAL/AML who had open-label HCT added to their treatment regimen. The remaining six completed studies (VAA A2401, VAA A2402, VAA A2403, VAH BUS04, VAH BDE13E1 and VAH B2406E1) were designed to evaluate various regimens of dual combinations and include exposure to the triple combination through the double-blind or optional, open-label addition of the third component during the late phase of the study. The safety data in the subgroup of patients exposed to triple therapy from these studies is considered supportive. There is one ongoing study (VAA AUS01) examining VAL/AML with the optional addition of HCT. Parameters related to diastolic function, ventricular size and function, and ventricular hypertrophy are being assessed. The below table summarises the main aspects of study VEA A2302 and VEA ABR01. However, the supportive study VEA ABR01 does not significantly contribute to clinical efficacy and further discussion will therefore focus mainly on study VEA A2302.

Protocol Study Dates Country	Study Design & Purpose Endpoints	Population	Treatment
VEA489A2302 An 8-week, multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of the combination of valsartan/HCTZ/amlodipine compared to valsartan/HCTZ, valsartan/amlodipine, and HCTZ/amlodipine in patients with moderate to severe hypertension			
Argentina, Canada, Denmark, Ecuador, Greece, Hong Kong, Norway, Peru, Portugal, Russia, Sweden, Turkey, UK, US, Venezuela start: 15 May 2006 end: 02 Aug 2007	Multicenter, randomized, double-blind, parallel group study to evaluate the efficacy and safety of the combination of VAL/AML/HCT compared to dual combinations (VAL/HCT, VAL/AML and HCT/AML) in patients with moderate to severe hypertension. Primary: Change from baseline in MSDBP and MSSBP. Secondary: overall BP control rate, diastolic and systolic BP control rates, diastolic and systolic BP response rates, change from baseline in standing BP, change from baseline in 24-hour mean ABPM. Safety: AEs/SAEs, laboratory values, urinalysis, PE, ECG, echocardiogram, pregnancy test	total: 2271 randomised, 2060 completed, 211 discontinued age: 19-84 (average 53.2 years) sex: 1255 male, 1016 female groups: 4	form: capsules & tablets route: p.o. regimen: o.d. duration: 4 weeks single-blind run-in and 8 weeks double blind treatment doses: VAL/AML/HCT 320/25/10 mg VAL/HCT 320/25 mg VAL/AML 320/10 mg HCT/AML 25/10 mg
VEA489ABR01 An open-label, randomized, multicenter study to evaluate the efficacy of the combination of valsartan and hydrochlorothiazide and amlodipine in hypertensive patients not controlled with valsartan and hydrochlorothiazide			
Brazil start: 21 Aug 2006 end: 31 May 2007	Open label, randomized, multicenter study to evaluate the efficacy of the combination of VAL+HCT+AML in hypertensive patients not controlled with VAL+HCT. Primary: overall BP control rate. Secondary: diastolic and systolic BP control rate, diastolic BP responder rate, mean change from baseline in MSDBP, MSSBP, and standing BP Safety: AE/SAE monitoring, physical examination, vital signs, laboratory evaluations (haematology and blood chemistry) and pregnancy testing, ECG evaluation	total: 340 enrolled dual therapy phase (safety population); 264 enrolled non-randomised triple therapy phase; 182 randomised triple therapy; Triple therapy patients: age: 29-81 (average 56.5 yrs) gender: 72 male, 192 female groups: 3 (1 non-randomized triple therapy; 2 randomized triple therapy)	form: tablet route: p.o. regimen: o.d. duration: 12 weeks (triple therapy) doses: VAL/HCT 160/12.5 mg o.d. (4 wk). Patients who did not meet BP target were force titrated to VAL/ HCT/AML 160/12.5/5 mg o.d. (4 wk). Patients who did not meet BP target were randomized to either VAL/HCT/AML 160/12.5/ 10 mg o.d. (4 wk) or VAL/HCT/AML 160/25/5 mg o.d. (4 wk). Patients who still did not meet BP target were force titrated to VAL/HCT/AML 160/25/10 mg o.d. (4 wk) Only patients who did not meet BP target continued in the study at each titration-step. Patients who met BP target were withdrawn as soon as the BP target was achieved.

METHODS

Study Participants

The VEA A2302 study population consisted of male and female patients ≥ 18 years and <86 years of age with moderate to severe hypertension who fulfilled one of the following requirements:

- Diagnosis of moderate to severe hypertension (MSDBP ≥ 100 mmHg and <120 mmHg, and MSSBP ≥ 145 mmHg and <200 mmHg) at Visit 3
- Patients also had to meet the blood pressure requirements (MSDBP ≥ 95 mmHg and <110 mmHg, and MSSBP <180 mmHg) at Visit 2
  or
- • MSDBP ≥ 110 mmHg and <120 mmHg, and MSSBP ≥ 145 mmHg and <200 mmHg, or MSDBP ≥ 100 mmHg and <110 mmHg and MSSBP ≥ 180 mmHg and <200 mmHg after one week of treatment with placebo (blood pressure check) or at any subsequent scheduled study visit or blood pressure evaluation during the single-blind run-in period (designated Visit 3)

The following conditions were amongst the main exclusion criteria:
- Inability to discontinue all prior antihypertensive medication for a period of 1 to 5 weeks.
- Patients with an MSDBP ≥ 120 mmHg or an MSSBP ≥ 200 mmHg at screening or any time during the single-blind run-in period; patients with an MSSBP ≥ 180 mmHg and MSDBP <100 mmHg at any time between one week (7 ± 3 days) and four weeks of treatment with placebo had to be discontinued from the study; patients on two or more antihypertensive drugs with MSSBP ≥ 180 mmHg and/or MSDBP ≥ 110 mmHg at Visit 1; patients on three or more antihypertensive drugs with MSDBP ≥ 90 mmHg and <110 mmHg, and/or MSSBP ≥ 140 mmHg and <180 mmHg at Visit 1.
- Patients with type 1 diabetes mellitus and those patients with type 2 diabetes mellitus who were not well controlled based on the investigator's clinical judgement.
- Known or suspected contraindications, including a history of hypersensitivity to angiotensin receptor blockers, thiazide diuretics, dihydropyridine calcium antagonists, or similar drugs.
- Any history of pancreatic injury, hepatic disease, oesophageal varices, renal impairment, etc.
- Other criteria

Treatments
The following study drugs were provided: valsartan 160 mg tablets, hydrochlorothiazide 12.5 mg, capsules, hydrochlorothiazide 25 mg capsules, amlodipine 5 mg capsules, amlodipine 10 mg capsules, placebo for the run-in period and matching placebo for each active study drug. On each day of the single-blind run-in and double-blind treatment periods patients took by mouth one dosage form (either a capsule or tablet) from each of four provided bottles. At Visit 1 and continuing throughout the study, patients took 2 tablets and 2 capsules at around 8am, except on days when clinic visits were scheduled.

Phase	**Pre-randomization**		**Study Drug Treatment**					
Period	**Single-blind run-in**[1]		**Double-blind treatment**					
Duration	(1-2 weeks)	(1-3 weeks)	(8 weeks)					
Visit	1	2	3	4	5	6	7	8
Week	-4	-2	1	2	3	5	7	9
Treatment	Placebo		Randomization					
			V/H/A[2]	V/H/A[3]	V/H/A[4]			
			0/12.5/5	0/12.5/5	0/25/10			
			160/12.5/0	160/12.5/0	320/25/0			
			160/0/5	160/0/5	320/0/10			
			160/12.5/0	160/12.5/5	320/25/10			

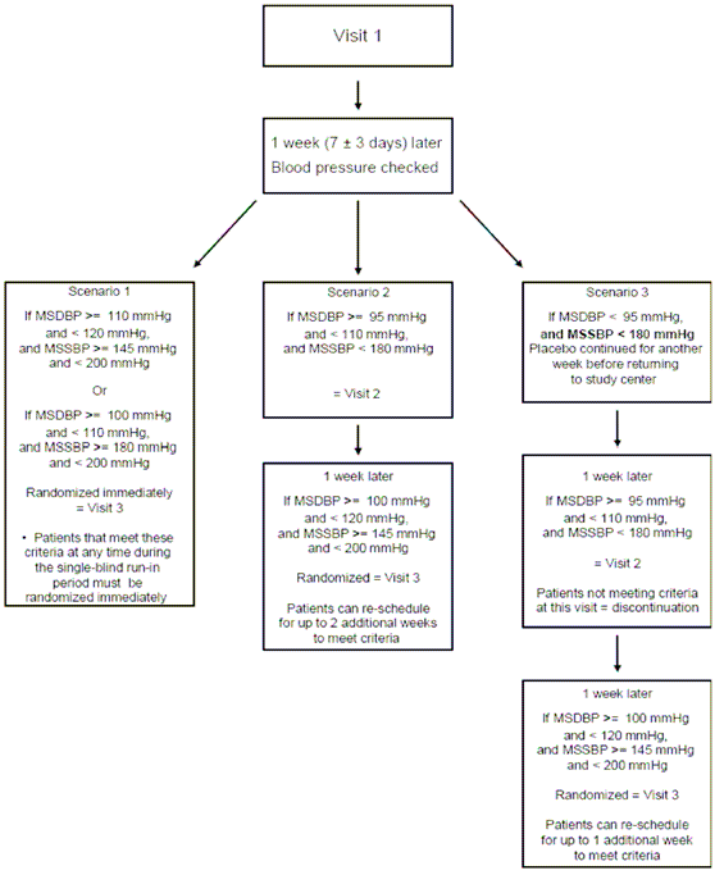
1 Patients on an antihypertensive medication at Visit 1 that required gradual withdrawal (according to the manufacturer's instructions, e.g. beta-blocker and/or clonidine) underwent a one week washout period prior to the start of the single-blind placebo run-in period.

2 Doses of valsartan, hydrochlorothiazide, and amlodipine during the first week of treatment in the double-blind period.

3 Doses of valsartan, hydrochlorothiazide, and amlodipine during the second week of treatment in the double-blind period.

4 Doses of valsartan, hydrochlorothiazide, and amlodipine during weeks 3 through the end of treatment in the double-blind period.

Patients in the pre-randomisation phase had their antihypertensive therapy withdrawn and entered the single-blind placebo run-in period for duration of 4 days to 4 weeks. Patients taking antihypertensive medication that required gradual withdrawal underwent a washout period prior to entering the placebo run-in period. All patients had a check of blood pressure at Visit 1 which determined their eligibility for randomization into the trial according to 3 scenarios described:



Objectives

Primary objectives in study VEA A2302: To demonstrate that at least one of the following two efficacy criteria was met:

- A once daily dosing regimen of the triple combination of VAL/HCT/AML was superior to the dual combinations of VAL/HCT, VAL/AML, and HCT/AML in lowering MSDBP in patients with moderate to severe hypertension.
- A once daily dosing regimen of the triple combination of VAL/HCT/AML was superior to the dual combinations of VAL/HCT, VAL/AML, and HCT/AML in lowering MSSBP in patients with moderate to severe hypertension.

Secondary objectives (triple combination *vs* dual combinations) in study VEA A2302:

- Blood pressure control rates (MSSBP/MSDBP <140/90 mmHg), diastolic blood pressure control rates (MSDBP <90 mmHg), systolic blood pressure control rates (MSSBP <140 mmHg), diastolic blood pressure responder rates (MSDBP <90 mmHg and/or ≥ 10 mmHg reduction from baseline), systolic blood pressure responder rates (MSSBP <140 mmHg and/or ≥ 15 mmHg reduction from baseline), decrease in 24-hour mean ambulatory diastolic and systolic blood pressures, safety and tolerability, pharmacokinetic drug interaction at steady state: plasma drug levels of VAL, HCT and AML achieved with the triple combination *vs* the dual therapies.

Outcomes/endpoints

The primary efficacy variables in trial VEA A2302 were change from baseline to endpoint (LOCF, week 5, week 7 and week 9) in MSDBP and in MSSBP. The secondary efficacy variables included overall control rate (MSSBP/MSDBP < 140/90 mmHg) at endpoint and at weeks 5, 7 and 9, diastolic control rate (MSDBP < 90 mmHg) at endpoint and at weeks 5, 7 and 9, systolic control rate (MSSBP < 140 mmHg) at endpoint and at weeks 5, 7 and 9, diastolic responder rate (MSDBP < 90 mmHg or ≥

10 mmHg reduction from baseline) at endpoint and at weeks 5, 7 and 9, systolic responder rate (MSSBP < 140 mmHg or ≥ 15 mmHg reduction from baseline) at endpoint and at weeks 5, 7 and 9, change from baseline in MSDBP and in MSSBP at weeks 5, 7 9, change from baseline to endpoint (LOCF) in standing diastolic and systolic BP, change from baseline to week 9 in post-dosing 24-hour mean ambulatory diastolic and systolic blood pressure (ADBP, ASBP), change from baseline to week 9 in daytime/night time mean ADBP and ASBP. The CHMP acknowledged that reductions from baseline to endpoint in trough MSDBP and MSSBP are recognised as valid surrogate markers for reduced risks of cardiovascular events. In addition, the chosen primary endpoint is in accordance with the CHMP guideline for second line therapy *Note for guidance on clinical investigation of medicinal products in the treatment of hypertension* (CPMP/EWP/238/95 Rev.2).

Sample size
It was planned to obtain 2024 completed patients (506 patients per arm). Assuming a maximum dropout rate of 10%, a total of 2252 patients were planned to be randomized into four treatment groups (563 patients per arm). The planned sample size of 506 completed patients (563 randomized patients) per treatment group would provide 90% power to obtain statistical significance for the triple *vs* all three dual therapies at the two-sided significance level of 0.025 for change from baseline in MSDBP, assuming the true treatment difference is 2 mmHg between the triple and each dual therapy and a common standard deviation of 8 mmHg for all treatment groups and would also provide 90% power to obtain statistical significance for the triple versus all three dual therapies at the two-sided significance level of 0.025 for change from baseline in MSSBP, assuming the true treatment difference is 3.5 mmHg between the triple and each dual therapy and a common standard deviation of 14 mmHg for all treatment groups. These considerations seem acceptable. In total, 2060 patients completed the study.

Randomisation
At the end of the single-blind placebo run-in period of study VEA A2302, patients were randomised in a double-blind fashion for a total of 8 weeks of treatment in an equal allocation (1:1:1:1) to one of four treatment arms: VAL/HCT/AML: 320/25/10 mg o.d., VAL/HCT: 320/25 mg o.d., VAL/AML: 320/10 mg o.d., or HCT/AML: 25/10 mg o.d. A patient randomisation list was produced by the IVRS. Randomisation was stratified by centre. The first two weeks post randomization was a two-stage forced titration period: At Visit 3, patients received lower doses of the study drugs and were force-titrated over a two-week period to the maximum doses of VAL/HCT/AML 320/25/10 mg o.d., VAL/HCT 320/25 mg o.d., VAL/AML 320/10 mg o.d., and HCT/AML 25/10 o.d. Treatment at the maximum doses continued for 6 weeks until the end of the study (Visit 5 to Visit 8). The choice of comparators is considered appropriate. The comparator arms represented two marketed combination products Diovan HCT and Exforge respectively. The third combination, HCT/AML is not available as a combination product. Randomisation procedure was deemed acceptable.

Blinding (masking)
Patients, investigator staff, persons performing the assessments and data analysts were blinded to the identity of the treatment from the time of randomisation until database lock, using the following methods: randomization data were kept confidential until unblinding, and were only accessible to authorised persons; treatment identity was concealed by the use of study drugs that appeared identical in packaging, labelling, and schedule of administration; appearance, weight and odour of each study drug and its matching placebo were identical. Unblinding occurred in emergency and at the end of the study. IVRS reported any emergency code breaks immediately to the clinical trial leader and monitor.

Statistical methods
The six pair-wise treatment comparisons (three for MSDBP and three for MSSBP) for the triple combination *vs* dual combinations specified for the primary efficacy variable were performed for the change from baseline to weeks 5, 7, and 9 using the same two-way ANCOVA model with treatment and region as factors, and baseline MSDBP or MSSBP as a covariate in the model. The 95% and 97.5% confidence intervals were provided for the differences between the triple and each of the dual therapies. Among the secondary analyses, the blood pressure control rates and responder rates were analyzed using logistic regression models. The subgroup of patients taking part in the ABPM sub-study had their ambulatory blood pressure data analysed using analysis of covariance ANCOVA

models for repeated measures to assess treatment effects on lowering ambulatory blood pressures. The ITT population was the primary efficacy population. The PP population was used to assess robustness of the primary efficacy analysis results. In general the pre-specified statistical plan seems acceptable.

RESULTS

Participant flow
A total of 4285 patients were enrolled into the single-blind period of the study VEA A2302. A total of 2272 patients completed the single-blind period; 2013 were discontinued. The most common reason for discontinuation from the single-blind period was that the subject condition no longer required study drug (did not meet the blood pressure criteria for randomisation: 1204 patients; 28.1%), abnormal test procedure results (295 patients; 6.9%) and withdrawal of consent (228 patients; 5.3%).

Patient disposition by treatment – double blind period (randomized population)

	Val/HCTZ/Aml 320/25/10 mg N=583 n (%)	Val/HCTZ 320/25 mg N=559 n (%)	Val/Aml 320/10 mg N=568 n (%)	HCTZ/Aml 25/10 mg N=561 n (%)	Total N=2271 n (%)
Completed	522 (89.5)	506 (90.5)	526 (92.6)	506 (90.2)	2060 (90.7)
Discontinued	61 (10.5)	53 (9.5)	42 (7.4)	55 (9.8)	211 (9.3)
Adverse event(s)	24 (4.1)	17 (3.0)	10 (1.8)	20 (3.6)	71 (3.1)
Subject withdrew consent	11 (1.9)	13 (2.3)	15 (2.6)	17 (3.0)	56 (2.5)
Lost to follow-up	8 (1.4)	11 (2.0)	10 (1.8)	6 (1.1)	35 (1.5)
Unsatisfactory therapeutic effect	4 (0.7)	6 (1.1)	0 (0.0)	7 (1.2)	17 (0.7)
Administrative problems	5 (0.9)	2 (0.4)	5 (0.9)	3 (0.5)	15 (0.7)
Protocol violation	9 (1.5)	1 (0.2)	2 (0.4)	2 (0.4)	14 (0.6)
Subject condition no longer requires study drug	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.1)
Abnormal laboratory value(s)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)

Of the total randomized population, 312 patients (13.7%) had protocol deviations that excluded them from the Per Protocol population. The most frequently occurring deviations (as reported in the triple therapy group) were incorrect time of blood pressure measurement, study drug interruption > 3 consecutive days prior to Visit 8/End of Study, and use of NSAIDs and/or Cox-2 inhibitors ≤ 72 hours prior to Visits 3 or 8/End of Study. The number of randomised patients was balanced across treatments groups as was the completion rate (89.5%-92.6%). The most frequent reason for discontinuation was the presence of adverse events (AEs).

Recruitment
Study VEA489A2302 was conducted in Europe, Asia, North and South America. Study was initiated and completed between May 2006 and August 2007. Per protocol exclusion and inclusion criteria were observed when recruiting patients for participation.

Conduct of the study
The study protocol was amended twice; the first amendment corrected formal errors and provided clearer instructions on certain study procedures. Additional medications that affect blood pressure or could potentiate the effects of AML were also excluded from the study. The second amendment added one exclusion criterion, clarified the method for determining pulse rate, and clarified the period for SAE reporting. No changes were made to the planned analysis. However, these analyses have been added after clinical database lock: figure of mean change from baseline in MSDBP and MSSBP by week and treatment, figure of mean ADBP and ASBP at baseline by hour and treatment, figure of mean ADBP and ASBP at endpoint by hour and treatment, figure of mean change from baseline to endpoint in ADBP and ASBP by hour and treatment, patient listings of mean 24-hour, daytime and nighttime of ADBP and ASBP by treatment. The amendments do not interfere with results credibility.

Baseline data

Summary of demographics by treatment in the randomized population are presented below.

Demographic variable	Val/HCTZ/Aml 320/25/10 mg N=583	Val/HCTZ 320/25 mg N=559	Val/Aml 320/10 mg N=568	HCTZ/Aml 25/10 mg N=561	Total N=2271
Sex					
Male	316 (54.2%)	303 (54.2%)	319 (56.2%)	317 (56.5%)	1255 (55.3%)
Female	267 (45.8%)	256 (45.8%)	249 (43.8%)	244 (43.5%)	1016 (44.7%)
Age group (<65; ≥ 65)					
<65	501 (85.9%)	483 (86.4%)	492 (86.6%)	478 (85.2%)	1954 (86.0%)
≥ 65	82 (14.1%)	76 (13.6%)	76 (13.4%)	83 (14.8%)	317 (14.0%)
Age group (<75; ≥ 75)					
<75	570 (97.8%)	552 (98.7%)	554 (97.5%)	553 (98.6%)	2229 (98.2%)
≥ 75	13 (2.2%)	7 (1.3%)	14 (2.5%)	8 (1.4%)	42 (1.8%)
Age (years)					
n	583	559	568	561	2271
Mean (SD)	53.3 (10.28)	53.1 (10.36)	52.8 (10.29)	53.6 (10.13)	53.2 (10.26)
Range	20-82	21-84	23-83	19-82	19-84
Race					
Caucasian	420 (72.0%)	412 (73.7%)	403 (71.0%)	392 (69.9%)	1627 (71.6%)
Black	98 (16.8%)	93 (16.6%)	91 (16.0%)	107 (19.1%)	389 (17.1%)
Asian	4 (0.7%)	6 (1.1%)	10 (1.8%)	7 (1.2%)	27 (1.2%)
Native American	3 (0.5%)	3 (0.5%)	8 (1.4%)	4 (0.7%)	18 (0.8%)
Pacific Islander	2 (0.3%)	2 (0.4%)	1 (0.2%)	0 (0.0%)	5 (0.2%)
Other	56 (9.6%)	43 (7.7%)	55 (9.7%)	51 (9.1%)	205 (9.0%)
Body Mass Index (kg/m^2)					
n	581	554	565	557	2257
Mean (SD)	32.2 (6.91)	32.3 (6.95)	31.8 (6.41)	31.5 (6.07)	32.0 (6.60)
Range	20-78	18-83	19-60	16-57	16-83

All the demographic variables are taken from Visit 1, except weight. Weight was measured at Visit 3 (Week 1). If Visit 3 weight value was not available, Visit 1 (screening) value was used. BMI is calculated.

Summary of baseline characteristics by treatment in the randomized population are summarised below.

Demographic Variable	Val/HCTZ/Aml 320/25/10 mg N=583	Val/HCTZ 320/25 mg N=559	Val/Aml 320/10 mg N=568	HCTZ/Aml 25/10 mg N=561	Total N=2271
MSDBP (mmHg)					
n	583	559	568	561	2271
Mean (SD)	106.4 (5.08)	106.2 (5.07)	106.6 (5.14)	107.1 (5.14)	106.5 (5.12)
Range	93-119	96-119	86-119	98-120	86-120
MSSBP (mmHg)					
n	583	559	568	561	2271
Mean (SD)	169.6 (14.49)	169.5 (13.81)	169.6 (13.70)	170.8 (14.25)	169.9 (14.07)
Range	145-200	144-200	140-200	142-200	140-200
Sitting pulse (bpm)					
n	583	559	568	561	2271
Mean (SD)	77.5 (11.99)	77.3 (12.24)	77.1 (12.21)	78.0 (12.23)	77.5 (12.16)
Range	48-128	43-133	37-156	42-126	37-156
Duration of hypertension (months)					
n	583	558	568	561	2270
Mean (SD)	99.8 (99.02)	107.9 (107.71)	106.2 (100.31)	107.5 (104.39)	105.3 (102.85)
Range	0-552	0-600	0-648	0-600	0-648
History of diabetes					
No	521 (89.4%)	499 (89.3%)	520 (91.5%)	515 (91.8%)	2055 (90.5%)
Yes	62 (10.6%)	59 (10.6%)	48 (8.5%)	46 (8.2%)	215 (9.5%)

Baseline is defined as the value at Week 1 (Visit 3/Day 1). The duration of hypertension and history of diabetes are from Visit 1.

In general the treatment groups were well balanced with regard to demographic factors. The mean age was 53.2 years. It is to be noted that the presentation of the elderly population is limited: ≥ 65 years of age ranged from 13.4%-14.1% and ≥ 75 years of age ranged from 1.3%-2.5%. This is of note as the elderly population represent a large proportion of the hypertensive patients. Baseline characteristics were comparable across treatment groups. Duration of hypertension was slightly lower in the triple combination group (99.8 months *vs* 105.3-107.9 months). Between 8.2% and 10.6% of the randomised population had a history of type 2 diabetes. Diabetes Mellitus type 1 was an exclusion criterion.

Numbers analysed
Numbers (percentage) of patients in the analysis populations of enrolled patients are presented in the table below.

	Val/HCTZ/Aml 320/25/10 mg N (%)	Val/HCTZ 320/25 mg N (%)	Val/Aml 320/10 mg N (%)	HCTZ/Aml 25/10 mg N (%)	Total N (%)
Enrolled population (ENR)					4285
Randomized population (RND)	583 (100.0)	559 (100.0)	568 (100.0)	561 (100.0)	2271 (100.0)
Intent-to-Treat population (ITT)	571 (97.9)	553 (98.9)	558 (98.2)	554 (98.8)	2236 (98.5)
Safety population (SAF)	582 (99.8)	559 (100.0)	566 (99.6)	561 (100.0)	2268 (99.9)
Per protocol population (PP)	471 (80.8)	449 (80.3)	469 (82.6)	443 (79.0)	1832 (80.7)
ABPM population (ABP)	67 (11.5)	69 (12.3)	71 (12.5)	76 (13.5)	283 (12.5)
PK population (PK)	536 (91.9)	520 (93.0)	524 (92.3)	520 (92.7)	2100 (92.5)

Of the 35 randomized patients excluded from the ITT population, 23 were excluded for not having at least one post-baseline efficacy measurement. The other 12 randomized patients were excluded because they were from a study site with critical GCP findings. Patients who did not complete the study, and/or had major protocol deviations were excluded from the per protocol population (439). Three randomized patients were excluded from the safety population for not having taken at least one dose of double-blind study drug. The numbers of excluded subjects are proportional between the groups (the ITT analyzable proportions of different arms are within 97.9-98.9%) and in the range to be expected in this type of patients/study.

Outcomes and estimation
Primary endpoints: Results of the within-treatment analysis showed that clinically relevant and statistically significant reductions from baseline in MSDBP and MSSBP were achieved at endpoint with all 4 treatments. The greatest reductions were observed with triple therapy. The within-treatment reductions at Weeks 5, 7 and 9 were similar to those achieved at endpoint. In all treatment groups, the full blood pressure lowering effect was seen at Week 5. At that point in the study, all patients had been on their maximum dose of double-blind study medication for two weeks. The treatment with highest dose lasted 6 weeks; maximum treatment effect was seen by Week 3 of maximum dose treatment (study week 5). The between-treatment comparison showed that triple therapy was clinically and statistically superior to all three dual therapies in reducing both diastolic and systolic BP at endpoint in the ITT population, as showed in the table below. Results of the between-treatment comparisons at Weeks 5, 7 and 9 were similar to those observed at endpoint for the ITT patients. Similar efficacy results at endpoint were also obtained for the PP population.

Within-treatment analyses for change from baseline to endpoint in mean sitting BP (mmHg) (ITT population)

Treatment	N	Mean change from baseline(SE)	95% CI for mean change from baseline	p-value
Diastolic BP				
Val/HCTZ/Aml 320/25/10 mg	571	-24.57 (0.395)	(-25.348, -23.797)	<0.0001 *
Val/HCTZ 320/25 mg	553	-19.40 (0.431)	(-20.250, -18.558)	<0.0001 *
Val/Aml 320/10 mg	558	-21.41 (0.394)	(-22.186, -20.639)	<0.0001 *
HCTZ/Aml 25/10 mg	554	-19.60 (0.407)	(-20.399, -18.801)	<0.0001 *
Systolic BP				
Val/HCTZ/Aml 320/25/10 mg	571	-39.37 (0.692)	(-40.725, -38.008)	<0.0001 *
Val/HCTZ 320/25 mg	553	-31.81 (0.739)	(-33.266, -30.362)	<0.0001 *
Val/Aml 320/10 mg	558	-33.37 (0.660)	(-34.668, -32.077)	<0.0001 *
HCTZ/Aml 25/10 mg	554	-31.87 (0.710)	(-33.264, -30.475)	<0.0001 *

Means and associated standard errors, confidence intervals, and p-values were provided by a paired t-test.
* Indicates statistical significance at 0.05 level.

Between-treatment comparisons for change from baseline to endpoint in mean sitting BP (mmHg) (ITT population)

Treatment (mg)	LSM change from baseline	LSM difference in change from baseline (SE)	p-value	Hochberg adjusted p-value
Diastolic BP				
Val/HCTZ/Aml 320/25/10	-24.74			<0.0001*
Val/HCTZ 320/25	-19.69	-5.05 (0.539)	<0.0001	
Val/Aml 320/10	-21.49	-3.25 (0.537)	<0.0001+	
HCTZ/Aml 25/10	-19.46	-5.28 (0.539)	<0.0001	
Systolic BP				
Val/HCTZ/Aml 320/25/10	-39.68			<0.0001*
Val/HCTZ 320/25	-32.04	-7.64 (0.848)	<0.0001	
Val/Aml 320/10	-33.50	-6.18 (0.846)	<0.0001+	
HCTZ/Aml 25/10	-31.48	-8.20 (0.848)	<0.0001	

Least square means and standard errors, confidence intervals, and p-values were provided by the ANCOVA model containing treatment and region as factors and centered baseline value as covariate. The Hochberg adjusted p-values are based on the maximum p-value for the three comparisons in MSDBP and the maximum p-value for the three comparisons in MSSBP. + Maximum p-values of the three comparisons. * Indicates statistical significance at 0.05 level.

The triple combination VAL/HCT/AML 320/25/10 mg induced clinically relevant reduction in both MSDBP and MSSBP which was statistically and significantly superior to VAL/HCT 320/25, VAL/AML 320/10 and HCT/AML 25/10. The observed efficacy was not influenced by gender, whereas the efficacy was less convincing when adjusting for age (≥65 years) and race (black racial subgroup population): MSDBP and MSSBP were numerically superior compared to all dual therapies, however, only statistically significantly superior (for both MSDBP and MSSBP) compared to the VAL/HCT dual combination (age ≥65 years) and VAL/HCT and VAL/ML (black racial subgroup population). The number of included subjects above the age of 65 years or belonging to the black subgroup population was, however low, why these results should be interpreted cautiously. The CHMP identified a limitations in the study design regarding the choice of the population, as it could be questioned whether the enrolled subjects represent the wide hypertensive population: the number of elderly patients was low (only 1.8% for subjects ≥ 75 years of age) and patients with ischemic heart disease and type 1 diabetes as well as patients with type 2 diabetes not being well controlled were excluded from the study. In addition, patients with renal impairment as measured by creatinine ≥ 1.5 x ULN were excluded. The CHMP requested a clarification and in response submitted by the applicant, post hoc analyses were presented, which indicated that efficacy and safety was comparable between patients with type 2 diabetes (9.5% of study population) and patients without diabetes. Similar results were given for patients with mild and moderate renal dysfunction, as well as the group of elderly ≥65 years. Furthermore clarifications concerned the fact highlighted by the CHMP that patients who might have responded to the lower doses of the triple and dual combinations were forced titrated to the maximum doses of the four therapies and the forced titration step of two weeks duration could have been too short to allow evaluation of the BP lowering effect of these lower doses. However, the

applicant presented arguments for the necessity of the short run-in phase, e.g. inclusion of patients with severe hypertension, and the issue was resolved.

Secondary endpoints:
Overall BP control rates: Overall BP control was defined as MSSBP/MSDBP < 140/90 mmHg. At each assessment during the double blind period, significantly greater proportions of patients receiving triple therapy achieved overall BP control compared with dual therapies. Significantly greater proportions of patients on triple therapy achieved overall BP control compared to dual therapies in both age groups (<65, ≥65 years), both genders and in the Caucasian and Black race subgroups.
Diastolic control rates: Diastolic control was defined as MSDBP<90 mmHg. At each assessment during the double blind period, significantly greater proportions of patients receiving triple therapy achieved diastolic BP control compared to those receiving any of the dual therapies.
Systolic control rates: Systolic control was defined as MSSBP<140 mmHg. At each assessment during the double blind period, significantly greater proportions of patients receiving triple therapy achieved systolic BP control compared to those receiving any of the dual therapies.
Diastolic responder rates: Diastolic response was defined as MSDBP<90mmHg or ≥10mmHg reduction from baseline. At each assessment during the double blind period, significantly greater proportions of patients receiving triple therapy achieved diastolic response compared to those receiving any of the dual therapies.
Systolic responder rates: Systolic response was defined as MSSBP<140mmHg or ≥15mmHg reduction from baseline. At each assessment during the double blind period, significantly greater proportions of patients receiving triple therapy achieved systolic response compared to any of the dual therapies.
Ambulatory blood pressure measurements: All four treatments produced clinically relevant and statistically significant reductions in mean 24-hour ambulatory blood pressure compared to the baseline. Triple therapy was statistically superior to all three dual therapies in reducing both 24-hour diastolic and systolic ABP at endpoint.
Standing blood pressure measurements: Within- and between-treatment reductions in standing diastolic and systolic BP were similar to those observed for the sitting measurements.

For all secondary endpoint measures of blood pressure control and response, the triple combination therapy was shown to be statistically superior to all three dual therapies as calculated by hazard ratios. In addition, reductions in 24-hour mean ambulatory systolic and diastolic blood pressure were clinically and statistically significantly greater with triple therapy compared to all three dual therapies. It could be argued that triple therapy with the same active substance given as dual+mono therapy administered in the morning and evening respectively, may result in a different 24-hour BP lowering profile. Therefore, the CHMP requested a statement in the SPC, which specifies that before switching to Exforge HCT, patients should be controlled on stable doses of the monocomponents taken at the same time. The recommended dose is one tablet per day, to be taken preferably in the morning.

Ancillary analyses
The pharmacokinetic analysis showed that the pre-dose concentrations of VAL, HCT and AML at steady state were comparable between the triple combination and the corresponding dual combination treatments. The plasma concentrations of the three components were determined at a steady state at pre dose at Visits 6 and 8 (Weeks 5 and 9). The concentrations of each analyte were compared between the triple combination treatment *vs* the corresponding dual combination treatments. The data were analyzed for each Visit (6 or 8/Week 5 or 9) and after pooling the data from two visits.

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

No pooled or meta-analyses were performed.

- Clinical studies in special populations

No studies in special populations were submitted, but primary measures in the pivotal study VEA A2302 were analysed by subgroups of study population. Between-treatment comparisons for change from baseline to endpoint in mean sitting BP were calculated according to age, gender and race (Caucasian and Black only). Gender had little effect on the efficacy of the triple combination. Age and race seemed both to have some influence on the efficacy. In patients aged 65 and over, numeric

superiority was present for all comparisons in both MSDBP and MSSBP, but statistical significance was only achieved in comparison to VAL/HCTZ. In black patients the superiority was significant for comparisons with VAL-containing combinations. As especially the elderly sub-group was small, the results are not conclusive. The results of the post-hoc analyses by concomitant diabetes and by high baseline systolic BP (MSSBP ≥180 mmHg) seem to indicate that the baseline SBP does not influence the efficacy results, but the diabetic status may influence the response, especially in comparisons with AML- containing dual therapies. This, however, is a post-hoc analysis in small number of diabetic patients and the results should be approached with caution.

Between-treatment comparisons for change from baseline to endpoint in mean sitting BP (mmHg) by diabetes status, Study VEA A2302 (ITT population)

Diabetes: yes **DBP/SBP Parameter** **Treatment (mg)**	**N**	**LSM change from baseline**	**LSM difference in change from baseline (SE)**	**p-value**
Diastolic BP				
VAL/HCT/AML 320/25/10	61	-23.23		
VAL/HCT 320/25	58	-17.47	-5.76 (1.811)	0.0017
VAL/AML 320/10	47	-22.91	-0.32 (1.918)	0.8664
HCT/AML 25/10	46	-20.95	-2.28 (1.927)	0.2375
Systolic BP				
VAL/HCT/AML 320/25/10	61	-38.66		
VAL/HCT 320/25	58	-27.88	-10.78 (2.998)	0.0004
VAL/AML 320/10	47	-34.52	-4.15 (3.188)	0.1949
HCT/AML 25/10	46	-36.63	-2.03 (3.248)	0.5327
Diabetes: no **DBP/SBP Parameter** **Treatment (mg)**	**N**	**LSM change from baseline**	**LSM difference in change from baseline (SE)**	**p-value**
Diastolic BP				
VAL/HCT/AML 320/25/10	510	-24.90		
VAL/HCT 320/25	494	-19.96	-4.93 (0.563)	<0.0001
VAL/AML 320/10	511	-21.37	-3.53 (0.559)	<0.0001
HCT/AML 25/10	508	-19.31	-5.59 (0.560)	<0.0001
Systolic BP				
VAL/HCT/AML 320/25/10	510	-39.84		
VAL/HCT 320/25	494	-32.48	-7.35 (0.879)	<0.0001
VAL/AML 320/10	511	-33.38	-6.45 (0.872)	<0.0001
HCT/AML 25/10	508	-30.96	-8.88 (0.873)	<0.0001

- Supportive study(ies)

Study VEA ABR01

This was a randomized, open label, multicenter, two arm, parallel group study conducted in Brazil. Male and female hypertensive adult outpatients ≥18 years of age were previously treated with a stable dose of up to two prior antihypertensive medications for a minimum of 2 months. The primary efficacy variable was the proportion of patients reaching BP control, which was defined by the patient's baseline cardiovascular risk after 12 weeks of treatment. The duration of the study including all phases was 17 weeks. Due to lower than expected BP control rates, the enrolment stopped at 340 patients. Of the 264 patients who received triple combination therapy, 233 (88.3%) completed at least one of the treatment phases. For all ITT patients who received triple therapy, the proportion of patients who achieved blood pressure control at endpoint (Week 12) was 61.0%. Blood pressure control rates at Week 12 were similar for both randomized treatments: 43.9% for VAL/HCT/AML 160/12.5/10 mg; 45.8% for VAL/HCT/AML 160/25/5 mg. The CHMP considered this trial of a limited value for efficacy evaluation, mainly due to its design. The trial was uncontrolled and not designed to compare the 2 groups of triple therapy (160/12.5/10mg *vs* 160/25/5mg) or to compare triple therapy with dual therapy, and furthermore, all patients were by design treated with 160/25/10mg at the end of the trial. Also, the number of patients within the different risk groups is small.

Study VAA A2201E1
This was a 52-week, multicenter, open-label extension study to study 2201 in patients with mild to moderate uncomplicated essential diastolic hypertension conducted in Europe and America. After successfully completing 8 weeks of double-blind treatment in protocol VAA A2201, patients with a MSDBP<90mmHg and MSSBP<140mmHg could continue treatment with VAL/AML in this extension, receiving either VAL/AML 80/2.5 mg o.d. or 80/5 mg o.d. for a period of four weeks. Subsequently, patients without symptomatic hypotension or significant peripheral oedema were force titrated to VAL/AML 160/5 mg o.d. or 160/10 mg o.d., respectively, for the remainder of the trial. Addition of HCT 12.5 mg was optional. The primary efficacy variable was the change from baseline in MSDBP at trough. Out of 1246 patients, 1075 (86.3%) completed the trial. This study was only a voluntary extension study without statistical testing and benefit of triple therapy is not evident as reductions in blood pressure in the relatively small subgroup of patients who added HCT were not greater than in patients who remained on dual therapy. This study can be used for safety evaluation (see section Clinical safety) but does not support efficacy of the triple combination.

Clinical safety

Safety assessment for the triple combination AML/VAL/HCT is based on one pivotal study and one supportive study that evaluated the triple combination. Safety data are also provided for 4 completed (3 short-term and one long-term) trials, in which patients had the option to add open-label HCT to VAL/AML, and for 3 completed short-term trials, in which patients added either double-blind or optional open-label AML to VAL/HCT or VAL to HCT/AML. At least 1789 patients were exposed to triple therapy in these studies. Deaths and SAEs are reported for one ongoing study (Study VAA AUS01) in which patients had the option to add open-label HCT to VAL/AML. No pooling of data was performed, as major differences in study designs and absence of adequate control preclude any meaningful interpretation of the pooled frequency of AEs or other pooled safety data across studies. Primary interpretation of AML/VAL/HCT safety is based on studies VEA A2302 and VEA ABR01.

- Patient exposure

The number of patients exposed to the triple combination AML/VAL/HCT is reasonably high, 1789 patients. The biggest contributor to the safety database is study VEA A2302. However, exposure to the highest dose is limited and the number of patients exposed over 6 months is small. There are no long-term exposure data for the highest dose. The data are also limited for elderly patients, as the number of patients aged ≥65 years in the triple therapy arm of the pivotal study was 82 and that of patients aged ≥75 years just 13. There were 52 patients aged ≥65 in the study VEA ABR01. A further drawback identified by the CHMP was the fact that some subpopulations likely to benefit most from a triple combination were excluded or underrepresented, since patients with known ischemic heart disease, patients with renal impairment (as measured by creatinine ≥ 1.5 x ULN), type 1 diabetic patients as well as type 2 diabetic patients not well controlled were excluded from the study. Very few elderly were included. Even more limited is the exposure to long-term (6-12 months) triple therapy and none of these were exposed to the high strength AML/VAL/HCT 320/25/10mg.

Exposure to study drug by treatment (safety population, study VEA A2302)

Duration of exposure (days)	VAL/HCT/AML 320/25/10 mg N=582	VAL/HCT 320/25 mg N=559	VAL/AML 320/10 mg N=566	HCT/AML 25/10 mg N=561	Total N=2268
Mean (SD)	53.7 (12.16)	53.9 (12.52)	55.0 (10.59)	54.1 (11.83)	54.1 (11.80)
Median	56.0	56.0	56.0	56.0	56.0
Range	1-87	1-161	1-104	1-92	1-161
Overall days of exposure by interval (n %)					
1 -7 days	14 (2.4)	7 (1.3)	8 (1.4)	10 (1.8)	39 (1.7)
8 - 14 days	7 (1.2)	10 (1.8)	6 (1.1)	10 (1.8)	33 (1.5)
15 – 28 days	15 (2.6)	20 (3.6)	8 (1.4)	12 (2.1)	55 (2.4)
29 - 42 days	16 (2.7)	20 (3.6)	13 (2.3)	17 (3.0)	66 (2.9)
43 - 49 days	16 (2.7)	7 (1.3)	11 (1.9)	6 (1.1)	40 (1.8)
50 - 56 days	288 (49.5)	260 (46.5)	291 (51.4)	269 (48.0)	1108 (48.9)
57+ days	226 (38.8)	235 (42.0)	229 (40.5)	237 (42.2)	927 (40.9)

- Adverse events

In Study VEA A2302, the most frequently reported adverse events (AEs) in the total safety population were peripheral oedema (5.7%), headache (5.4%), and dizziness (5.2%). Dizziness occurred more often with triple therapy (7.7%) and VAL/HCT (7.0%) than with VAL/AML (2.3%) or HCT/AML (3.9%). Peripheral oedema occurred more often with HCT/AML (8.9%) and VAL/AML (8.5%) than with triple therapy (4.5%) or VAL/HCT (0.9%). Frequencies of other AEs were similar across treatment groups, as shown in the table below.

Adverse events (≥2% in VAL/HCT/AML group), regardless of study drug relationship, by preferred term and treatment (safety population, Study VEA A2302)

	VAL/HCT/AML 320/25/10 mg N=582	VAL/HCT 320/25 mg N=559	VAL/AML 320/10 mg N=566	HCT/AML 25/10 mg N=561	Total N=2268
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any preferred term	263 (45.2)	253 (45.3)	254 (44.9)	271 (48.3)	1041 (45.9)
Dizziness	45 (7.7)	39 (7.0)	13 (2.3)	22 (3.9)	119 (5.2)
Edema peripheral	26 (4.5)	5 (0.9)	48 (8.5)	50 (8.9)	129 (5.7)
Headache	25 (4.3)	30 (5.4)	28 (4.9)	39 (7.0)	122 (5.4)
Dyspepsia	13 (2.2)	5 (0.9)	6 (1.1)	2 (0.4)	26 (1.1)
Fatigue	13 (2.2)	15 (2.7)	12 (2.1)	8 (1.4)	48 (2.1)
Muscle spasms	13 (2.2)	7 (1.3)	7 (1.2)	5 (0.9)	32 (1.4)
Back pain	12 (2.1)	13 (2.3)	5 (0.9)	12 (2.1)	42 (1.9)
Nasopharyngitis	12 (2.1)	13 (2.3)	13 (2.3)	12 (2.1)	50 (2.2)
Nausea	12 (2.1)	7 (1.3)	10 (1.8)	12 (2.1)	41 (1.8)

Adverse events classified as severe occurred in 3.0% of the total safety population and at similar rates across treatment groups. AEs potentially related to low blood pressure occurred at very low frequencies, apart from dizziness. Hypotension occurred more often in the triple therapy group (1.5%) and the VAL/HCT group (1.4%) than in the VAL/AML or HCT/AML treatment groups. Otherwise, frequencies were similar across treatment groups.

The incidence of AEs suspected to be related to study treatment ranged from 14.3-22.9% across the treatment groups. The preferred terms most frequently suspected to be study drug related were those known to be associated with the various monotherapies. Dizziness occurred more often with triple therapy and VAL/HCT compared to the other two treatments.

Number (percent) of patients with suspected study drug-related adverse events by preferred term (greater than or equal to 2 percent for any treatment group; safety population, study VEA A2302)

Preferred term	Val/HCT/AML 320/25/10 mg N=582 n (%)	Val/HCT 320/25 mg N=559 n (%)	VAL/AML 320/10 mg N=566 n (%)	HCT/AML 25/10 mg N=561 n (%)	Total N=2268 n (%)
All AEs suspected to be study drug related	133 (22.9)	80 (14.3)	90 (15.9)	112 (20.0)	415 (18.3)
Dizziness	29 (5.0)	23 (4.1)	5 (0.9)	11 (2.0)	68 (3.0)
Edema peripheral	19 (3.3)	2 (0.4)	35 (6.2)	41 (7.3)	97 (4.3)
Headache	9 (1.5)	7 (1.3)	2 (0.4)	12 (2.1)	30 (1.3)
Edema	6 (1.0)	0 (0.0)	13 (2.3)	11 (2.0)	30 (1.3)

** Preferred terms are sorted by total incidences (descending) in the VALl/HCT/AML treatment group*

Additional analyses of peripheral oedema and oedema (pooled terms) were performed in this pivotal study, because oedema is a known common side effect of AML. As shown in the table below, the incidence of peripheral oedema with triple therapy was statistically significantly less than that reported with VAL/AML and HCT/AML but greater than that reported with VAL/HCT. It is noted that the incidence of oedema may be considerably higher: in study VEA ABR01 the incidence of oedema in patients on triple therapy randomised to treatment was 35.2% for VAL/HCT/AML 160 mg/12.5 mg/10 mg and 21.3% for VAL/HCT/AML 160 mg/25 mg/5 mg.

Comparison of peripheral oedema occurrence between treatment groups (safety population, study VEA A2302)

Treatment comparison (A *vs* B, mg)	Treatment A n/N (%)	Treatment B n/N (%)	p-value
VAL/HCT/AML 320/25/10 *vs* VAL/HCT 320/25	26/582 (4.5)	5/559 (0.9)	0.0002 *
VAL/HCT/AML 320/25/10 *vs* VAL/AML 320/10	26/582 (4.5)	48/566 (8.5)	0.0057 *
VAL/HCT/AML 320/25/10 *vs* HCT/AML 25/10	26/582 (4.5)	50/561 (8.9)	0.0029 *

In the long-term study (2201E1) the most frequently reported AEs were peripheral oedema, nasopharyngitis, dizziness, headache and back pain. Peripheral oedema occurred at an incidence of 17.1% in the higher dose and 9.7% in the lower dose group. There were no severe AEs reported in patients who received VAL/HCT/AML 80 mg/12.5 mg/2.5 mg, whereas 7 patients (4.7%) who received VAL/HCT/AML 160 mg/12.5 mg/5 mg had severe AEs. In the high dose group, severe AEs were reported by 3 patients (16.7%) who received VAL/HCT/AML 80 mg/12.5 mg/5 mg and 4 patients (4.1%) who received VAL/HCT/AML 160 mg/12.5 mg/10 mg.

- Serious adverse event/deaths/other significant events

No deaths occurred in the completed studies and there were no deaths in the long-term study VAA A2201E1 among patients who received triple therapy of VAL/HCT/AML.

In the pivotal study VEA A2302, 21 patients (0.9%) experienced at least one SAE. Of the 47 SAEs reported, all occurred at similar frequencies across treatment groups, and were not clustered in any particular system organ class. Most patients (76%) were hospitalized as a result of their SAEs. Slightly more than half (52%) were discontinued, and 43% recovered from all of their events. In most cases (72%), the investigator did not suspect a relationship between the events and study drug. Five patients in the triple therapy group experienced SAEs. One patient had a study drug related hypokalaemia and another subject experienced several SAEs: abasia, neuropathy, abnormal coordination, asthenia and acute renal failure; all suspected to be study drug related; hyponatremia, urinary tract infection, rhabdomyolysis, fungal rash, chronic obstructive pulmonary disease and hypomagnesemia, none of which were suspected to be study drug related. One patient had a study drug unrelated myocardial infarction, coronary artery disease and angina pectoris. Another patient had study drug unrelated pancreatitis, nausea and abdominal pain, none of which were suspected to be study drug related. One patient had a cerebrovascular accident and muscular weakness, neither of which was suspected to be study drug related. These 5 patients were discontinued as a result of one or more SAEs, and 4 of them were hospitalized.

In the supportive study VEA ABR01, 2 patients (2.1%) had SAEs and both were in the VAL/HCT/AML 160/25/5 mg group. Both patients were hospitalized, but neither was discontinued. None of these events was suspected to be study drug related. Out of the total safety population of 1246 patients in the long-term study VAA A2201E1, 49 (3.9%) had SAEs, five of whom were taking triple therapy. None of these events was suspected to be study drug related.

Furhermore, the SPC for Exforge HCT reflects the contraindications identified for the monocomponents.

- Laboratory findings

No unexpected laboratory abnormalities were noted for patients treated with triple therapy. The largest number of patients with clinically notable abnormalities was an increase in BUN where the greatest incidence was in the VAL/HCT/AML and the VAL/HCT groups. There was generally greater incidence of increases in creatinine, uric acid, and calcium in groups receiving HCT. Mean potassium decreased in all treatment groups containing HCT with the greatest decrease in the HCT/AML group (-0.39 mmol/L) and smaller decreases in the VAL/HCT/AML (-0.16 mmol/L) and the VAL/HCTZ (-0.08 mmol/L) groups. The counteracting effects of VAL 320 mg and HCT 25 mg on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant. Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals as reflected in the SPC.

Periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals to detect possible electrolyte imbalance, especially in patients with other risk factors such as impaired renal function, treatment with other medicinal products or history of prior electrolyte imbalances.

- Safety in special populations

No special population studies were performed. Subgroup evaluations of AEs were conducted for the pivotal study by age, gender, race and diabetic status. No specific characteristics were found for any of these subgroups. The overall incidence of AEs was lower in elderly patients (≥ 65 years) than in younger patients in the triple therapy group. Dizziness occurred at similar rates in elderly and younger patients in the triple therapy group and was higher in elderly patients in the triple therapy group (7.3%) compared to elderly patients in the dual therapy groups (3.9-5.3%). Peripheral oedema rates were similar between elderly and younger patients within each treatment group. The incidence of peripheral oedema was less in both elderly and younger patients in the triple therapy group compared to the same subgroup in the other dual therapy groups containing AML. It should be noted, however, that only 14% of patients in the pivotal study were above 65 years. Only 14 patients (2.2%) were >75 years. No dose adjustment of Exforge HCT is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m^2), but periodic monitoring of serum potassium, creatinine and uric acid is recommended.
There is no experience on the use of AML/HCT/VAL in pregnancy. Based on the existing data with the components, the use of Exforge HCT is not recommneded during first trimester and contra-indicated during the second and third trimester of pregnancy.

- Safety related to drug-drug interactions and other interactions

No studies were conducted to evaluate drug interactions with the triple therapy of VAL/HCT/AML and other concomitant medications. Drug interactions reported for each of the individual mono-components is contained in the current prescribing information for VAL, HCT and AML, and are also reflected in the SPC of the triple combination AML/HCT/VAL.

- Discontinuation due to adverse events

In the pivotal study VEA A2302, AEs that led to discontinuation occurred in 3% of patients in the safety population (VAL/HCT/AML, 4.0%; HCT/AML, 3.4%; VAL/HCT, 2.9% and VAL/AML, 1.6%). The most common AEs leading to discontinuation in the triple therapy group were dizziness and hypotension. The incidence of discontinuations due to dizziness was 1.0% on triple therapy, 1.1% on VAL/HCT, 0.4% on VAL/AML, and 0.2% on HCT/AML. Hypotension led to the discontinuation in 0.7% of patients on triple therapy, and 1.1% on VAL/HCT. Peripheral oedema led to the discontinuation in 0.2% of patients on triple therapy, 0.4% on VAL/AML and 0.9% on HCT/AML. Overall, discontinuations due to AEs did not appear to be more frequent in triple therapy in comparison with double combinations, although there may be a slightly increased risk of discontinuation due to hypotension related effects in the triple therapy patients. Nevertheless, the absolute number of discontinuations is not sufficient to draw firm conclusions.

- Post marketing experience

The VAL/AML/HCT fixed triple combination is currently not marketed; however, limited safety data are available from the safety database on the use of free combination of this triple combination. The search performed on all AEs reported for VAL administered with AML and HCT as co-medication up to the cut-off date of May 2008 retrieved 129 case reports that matched the proposed criteria with 648 events classified according to MedDRA preferred terms and respective System Organ Class. One patient may have experienced several events. The mean number of events per case is 5.02. The reported events are already included in the prescribing information for the mono-components of VAL/HCT/AML for which causality can be explained by co-medications, co-morbidities or underlying disease.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system, version 2.0, as described by the applicant fulfils the legislative requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction of occurring either in the Community or in a third country.

Risk Management Plan

The CHMP did not require the MAA to submit a risk management plan for AML/VAL/HCT fixed combination and this was not proposed by the applicant based on the following rationale:

- Considerable safety information is available on individual components (AML, VAL, HCT) and two double combination products (VAL/HCT and AML/VAL). This safety information is well documented and communicated to regulators and health care professionals. This should contribute to the minimisation of the risk of the triple combination.
- No new safety concern emerged during the pre-clinical and clinical development program of the combination product of AML/VAL/HCT.
- The proposed SPC contains the relevant safety information about AEs observed during the clinical development programme in addition to AEs present in the SPC of its individual components. Thus, the proposed SPC contains the relevant information needed to minimise risks associated with the use of the triple combination in clinical practice.

The applicant is committed to continuous risk/benefit evaluation of Exforge HCT once placed on the market. Ongoing routine pharmacovigilance programs are to be implemented for screening safety data for any new potential or identified signals for the mono-components and the double combinations. Similar programme will be initiated for Exforge HCT. New safety information derived from routine pharmacovigilance activities will be evaluated and need for further action assessed in collaboration with the Health Authorities.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the opinion, there are some unresolved quality issues, which don't have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

The combination consists of three well-described compounds, amlodipin, valsartan and hydrochlorothiazide. The pharmacology of the triple combination has not been investigated; however, it is deemed acceptable due to the pre-clinical and clinical knowledge of the individual compounds and the combinations of VAL/AML and VAL/HCT. The literature overviews supported the concept that a combination therapy with VAL, HCTZ and AML elicits synergistic effects on blood pressure control and associated alterations in the vascular system and heart. It is suggested that these benefits would also be obtained in hypertensive patients, including those with co-morbidities such us diabetes. Nevertheless, the pharmacovigilance system put in place will ensure detection of any safety signals, should these arise in clinical practice.

Due to the distinct mechanisms of action of these classes of drugs, the combination therapy is anticipated to be more effective than the monotherapy. The pharmacokinetics of the triple combination was investigated as part of the toxicokinetics of the pivotal repeat-dose toxicity study. The

pharmacokinetic profiles of the mono-components are well known. Even though differences in pharmacokinetics/toxicokinetics could not be completely excluded in the 13-week toxicity study, the lack of pharmacokinetic interactions between the three compounds has been confirmed by clinical data. Toxicological evaluation of the triple combination of AML/VAL/HCT comprising of two dose toxicity study and 2- and 13-week repeat dose toxicity studies in the rat showed gastrointestinal inflammation with focal glandular erosions and histopathological changes in the kidney, most probably due to the local irritation caused by VAL. Co-administration did not show an impact on the toxicokinetics of HCT and AML, while an effect on the toxicokinetics of VAL cannot be excluded due to the higher exposure to VAL in combination when compared to monotherapy. VAL and AML are non-genotoxic compounds. HCT has been safely used for several decades and although the genotoxic potential cannot be entirely excluded, the lack of further information is exceptionally deemed acceptable as the *in vitro* and *in vivo* genotoxicity studies indicate unlike genotoxicity, and the compound has been extensively used in clinical practice for a long time. Reproductive toxicity has previously been assessed for AML and VAL and the recommendation for the products use in pregnancy are similar to that for the marketed AML/VAL combination. No specific carcinogenicity or local tolerance and other toxicity studies have been conducted which is in line with applicable guidelines. The Environmental Risk Assessment was proved incomplete and thus, there are currently a number of post-authorisation follow-up measures agreed in order to effectively assess the impact of AML/VAL/HCT on the environment.

Efficacy

The prevalence of hypertension in Europe ranges from 20-30% in the 3rd and 4th decades of life to more than 70% in the age group of patients over 65 years. Majority of patients need combination treatment to control their blood pressure. This is also reflected in the patterns of medicine use. The current product, Exforge HCT, is a combination of 3 active substances from 3 different drug classes, each of which is recommended as an option for the first line treatment of essential hypertension. Efficacy of the mono-components and two dual combinations (VAL/HCT, VAL/AML) has been proven in the past. Two completed studies assessed the efficacy and safety of the AML/VAL/HCT combination: the pivotal VEA A2302 study and the supportive VEA ABR01 study. Some long-term data were provided in the extension study A2201E1.

Study VEA A2302 evaluated the efficacy and safety of once-daily treatment with the combination of VAL/HCT/AML 320/25/10 mg compared to 3 dual therapies: VAL/HCT 320/25 mg, VAL/AML 320/10 mg, and HCT/AML 25/10 mg in hypertensive patients. The patients (n=2271) suffered from moderate to severe hypertension, i.e. grade 2 and 3 hypertension based on the Task force for the management of hypertension of the European society of hypertension (ESH) and the European society of cardiology (ESC). This study population represented the target population for triple antihypertensive therapy. It is however, noted that the presentation of the elderly population is limited and patients with some co-morbidities, e.g. type 1 diabetes mellitus, heart disease, were excluded. Following the pre-randomisation phase, patients were randomised to a triple combination VAL/HCT/AML 320/25/10 mg or the dual combinations of VAL/HCT 320/25 mg, VAL/AML 320/10 mg, and HCT/AML 25/10 mg. The treatment phase was initiated by a two-week forced-titration to achieve the maximum once-daily doses of study treatment. Treatment with the highest dose strength continued for an additional 6 weeks. All doses used in the study, whether as monotherapy or combination therapy, are approved for the treatment of hypertension. At week 8, the triple combination therapy was statistically superior to each of the three dual combination treatments in reduction of diastolic and systolic blood pressures. The reductions in systolic/diastolic blood pressure with Exforge HCT were 7.6/5.0 mmHg greater than with VAL/HCT, 6.2/3.3 mmHg greater than with AML/VAL, and 8.2/5.3 mmHg greater than with AML/HCT. The full blood pressure lowering effect was achieved 2 weeks after being on their maximal dose of Exforge HCT. Statistically greater proportions of patients achieved blood pressure control with Exforge HCT compared to each of the three dual combination therapies. The observed efficacy was not influenced by gender, whereas the efficacy was less convincing when adjusting for age (≥ 65 years) and race (black racial subgroup population). Although the observed effect on blood pressure is of clinical relevance and the triple combination therapy is of greater convenience compared to 3 single or dual + single therapies, the number of included subjects above the age of 65 years or belonging to the black subgroup population

was, however low, and considering the exclusion of patients with comorbidities, the results should be treated with caution. Generally, increase in patient treatment compliance is expected.

Safety

The safety database is mainly based on 582 hypertensive patients who received triple therapy with VAL/HCT/AML in the pivotal study VEA A2302. Furthermore there are safety data from 960 additional hypertensive patients who received triple therapy in 7 other unrelated trials. At least 247 and up to 271 patients received triple therapy for 6-12 months where HCT 12.5 mg was optionally added to VAL/AML 160/5 mg or 160/10 mg. There is no long term data on the highest strength with VAL 320 mg. In the pivotal study where the maximum dose of VAL/HCT/AML was studied, the overall incidence of AEs was similar in patients receiving triple therapy compared to patients receiving dual therapy. The most common AEs in the triple therapy group were dizziness, peripheral oedema, and headache. There were no deaths; discontinuation due to AEs did not appear to be more frequent with triple therapy. Although no new safety signals were identified with triple therapy, the long-term data for the high strength containing VAL 320mg were lacking. Based on the submitted post-marketing experience with the use of VAL, the exposure for VAL 320 mg, and VAL 320 mg with HCT in Europe (as well as globally) represents a minor part of the overall exposure to VAL, but is regarded as sufficient to document "widespread use". Furthermore, the prescriptions for VAL 320 mg and VAL 320mg with HCT have been increasing almost constantly in the past 2 years. The 320 mg VAL dose is fairly well represented and the elderly patients, including those over 75 years of age. In addition, results from the new subgroup analyses of the pivotal study VEA A2302 for elderly $\geq$65 years, type 2 diabetic patients, patients with mild and moderate renal impairment and patients with severe systolic hypertension are generally reassuring for both efficacy and safety for these subgroups. Caution is advisable due to the small patient numbers, especially patients with ischemic heart disease, type 1 diabetes and patients $\geq$ 75 years.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics along with the data available from the use of the mono-coponents.

- User consultation

The overall quality of the user testing of the package leaflet for Exforge HCT is considered acceptable. The overall quality of the methodology and evaluation is positive. The weaknesses identified by the CHMP were addressed appropriately and the Patient Information Leaflet is considered to contain all necessary information.

Risk-benefit assessment

The main benefit of the product is the assumed better compliance with antihypertensive therapy when the pill burden is reduced in patients who are using triple therapy with amlodipine, valsartan and hydrochlorothiazide free combination. Bioequivalence for the lower dose strengths of the triple combination was proven and there is a wide therapeutic experience in their use. In line with the 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 CV treatment and prevention*, proof of bioequivalence between the fixed combination and its mono-components is sufficient provided drugs with a wide therapeutic experience and an adequately established benefit/risk ratio are concerned. From this point of view, no objections exist against the lower strengths of the fixed combinations:
VAL/HCT/AML 160/12.5/5 mg
VAL/HCT/AML 160/12.5/10 mg
VAL/HCT/AML 160/25/5 mg
VAL/HCT/AML 160/25/10 mg

With respect to the replacement indication for the highest dose VAL/HCT/AML 320/25/10 mg, further efficacy and safety data were necessary. The pivotal study with the triple combination VAL/HCT/AML 320/25/10 mg induced a reduction in both MSDBP and MSSBP which was

statistically significantly superior to VAL/HCT 320/25 mg, VAL/AML 320/10 mg and HCT/AML 25/10 mg. The main risks relate to the limited data available on the use of VAL 320 mg and the characteristics of the pivotal study population. Nevertheless, there is increasing evidence based on the prescription data showing an increase in the use of VAL 320 mg in the majority of EU countries. In addition, the substitution indication for Exforge HCT guarantees that only patients already treated with the free combination of AML, VAL and HCT will be given the fixed combination product.

A risk management plan was not submitted. The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Exforge HCT in the treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual-component and a single-component formulation was favourable and therefore recommended the granting of the marketing authorisation.