SCIENTIFIC DISCUSSION

1. Introduction

The proper management and control of blood pressure in hypertension patients, and the impact it has on associated morbidity and mortality rates, has been the focus of many new hypertension observational studies and clinical trials. These trials have demonstrated that more aggressive blood pressure lowering will reduce the complications associated with hypertension. As a result of this data, international guidelines for the management of hypertension now recommend a target blood pressure of <140/90 mmHg for most hypertensive patients, with even a lower blood pressure goal of <130/80 mmHg for high-risk patient populations such as patients with target organ damage, diabetes or renal disease. Despite the availability of many newer antihypertensive agents, hypertensive patients remain at higher risk of premature death than the general population. This persistence of morbidity and mortality may be accounted for by the frequent failure to achieve adequate blood pressure reduction despite an extensive array of available antihypertensive agents. Such considerations have led to reassessment of the potential role of fixed-dose combination agents in the antihypertensive armamentarium. The rationale for combination therapy relates to the concept that antihypertensive efficacy may be enhanced when 2 classes of agents are combined. In addition, combination therapy may enhance tolerability: first of the active substance of a fixed combination can antagonize some of the adverse effects of the second one. Fixed-dose combination therapy simplifies the treatment regimen, may prevent treatment failures that might result from missed doses. It has been recognized in the 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension that one of the rational combinations is the combination of a renin-angiotensin system antagonist, such as an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), with a calcium channel blocker (CCB). Both ACE inhibitors and CCBs lower blood pressure by reducing peripheral resistance, but calcium influx blockade and reduction of angiotensin II vasoconstriction are complimentary mechanisms. The edema induced by dihydropyridine CCBs results from the increased capillary hydrostatic pressure from pre-capillary vasodilatation. ACE inhibitors produce postcapillary vasodilatation thereby normalizing transcapillary pressure and reducing edema. The same mechanism of action of angiotensin receptor blockade would be expected to produce similar effects. Support for the rationale of the combination of a renin-angiotensin system antagonist and a CCB comes from the recently completed Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). In this trial in hypertensive patients with at least three cardiovascular risk factors, the CCB-based regimen of amlodipine and perindopril produced reductions in the risk of stroke by 23%, total cardiovascular events and procedures by 16%, all-cause mortality by 11%, and development of diabetes by 30% compared to a beta-blocker-based regimen of atenolol and bendroflumethiazide (Dahlof, et al (2005)). Valsartan, an orally active angiotensin II receptor blocker (ARB), was first developed for the treatment of hypertension and was approved for this use alone or in combination with other antihypertensive agents in once daily doses of 80 mg – 320 mg in the United States and 80 mg-160 mg in Europe and many other countries. It has been marketed for hypertension as monotherapy since 1996 and in combination with hydrochlorothiazide since 1997. Subsequently, valsartan has also been approved for the treatment of patients with chronic heart failure and patients with post-myocardial infarction in many countries. As described in the original valsartan monotherapy submission, adverse experiences have generally been mild and transient in nature and only infrequently require discontinuation of therapy. The overall incidence of adverse experiences with valsartan is similar to placebo. The most common reasons for discontinuation of therapy with valsartan are headache and dizziness. Amlodipine, a dihydropyridine calcium channel blocker (DHP-CCB), is approved for the treatment of hypertension, angina, and in some countries angiographically documented coronary artery disease and is available in doses of 5 and 10 mg and in some countries in a 2.5 mg dose for once daily administration. Amlodipine administered as monotherapy is generally well tolerated at doses up to 10 mg daily. Some of the more common side effects of dihydropyridine CCBs, including amlodipine, based on their pharmacologic site of action, include headache, and other dose dependent effects such as edema, dizziness, flushing, and palpitations.

This is the application for Exforge, a fixed dose combination (FCP) of amlodipine besylate and valsartan in the strengths of 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg using the centralised procedure. Approved product is indicated in patients whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy. This is an application for the centralised procedure. The application is submitted in accordance with article 10 b (fixed combination application) in Directive 2001/83/EC. The complementary mechanisms of an ARB and DHP-CCB are expected to provide superior antihypertensive efficacy as compared to the respective monotherapies.

2. Quality aspects

Introduction

Exforge is a fixed combination containing two active substances: amlodipine (as the besilate salt) and valsartan and is presented as film-coated tablets. The tablets contain 5/80 mg, 5/160 mg or 10/160 mg of amlodipine and valsartan respectively. It is packaged in PVC/PVDC blister packs or PA/AL/PVC blister packs.

Active Substance

Amlodipine besilate
Amlodipine besilate is the INN for the chemical substance 3- Ethyl- 5- methyl (4*RS*)- 2- [(2- aminoethoxy) methyl]- 4- (2- chlorophenyl)- 6- methyl- 1, 4- dihydropyridine- 3, 5- dicarboxylate benzenesulphonate (anhydrous substance). The molecular formula is $C_{26}H_{31}ClN_2O_8S$ ($C_{20}H_{25}ClN_2O_5 \cdot C_6H_5SO_3H$) and the relative molecular mass 567.06. A monograph for amlodipine besilate is adopted in 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. The compound has 2 pKa's: 9 and 0.4. and the distribution coefficient is log P_{ow}=2.76. No solid-state polymorphism of amlodipine besilate is described in the literature.

- Manufacture

Two sources of API are used, one with a CEP and one with an ASMF and a CEP.

- Specification

The satisfactory quality of both sources is generally ensured through the CEP, although additional tests are also applied (e.g. particle size (laser light diffraction), identification (X-ray powder diffraction), heavy metals (ICP/OES) and residual solvents (GC), specific limits for any impurity other than those mentioned in the Ph.Eur monograph). One of the manufacturers has identified an extra impurity not included in the Ph.Eur. monograph and the proposed limit for this impurity has been qualified with reference to toxicological studies, batch analyses and stability data. The proposed limit for this impurity has been justified according to the batch analyses and stability data. The results of the batch analysis presented for 3 batches purchased from each manufacturer are comparable and comply with the proposed specification that are considered adequate to control the substance on a routine basis.

- Stability

For one of the manufacturers, data for 3 batches stored for 48 months at 25 °C /60 % RH and at 40 °C /75 % RH for 6 months in the proposed market packaging were presented. The following parameters were investigated: appearance, water, assay and related substances, and results were well within the specification limits and showed no significant changes either in accelerated or in normal conditions.
The forced degradation light stress testing showed that amlodipine besilate is sensitive to light both as powdery substance and in water solution, whereas confirmatory stability testing study demonstrated that the immediate/ marketing packaging sufficiently protects the active substance from light.
The re-test period proposed by the manufacturer for amlodipine besilate was considered acceptable if stored in well-closed containers, protected from light.

For the other manufacturer, amlodipine besilate the re-test period is not specified on the CEP. Therefore, the applicant will analyse the active substance each time before the production of the finished product.

Active Substance

Valsartan

The manufacture, control and stability of valsartan have already been assessed for the original authorised medicinal product Diovan.

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. 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 the pure (S)-enantiomer is essentially used. The assigned (S)-configuration is defined from the synthetic origin ((L)-valine).
Its optical activity is $[\alpha]_{D/20}$ = -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 four consecutive synthetic steps and one auxiliary step for reagent preparation. Purification is achieved by recrystallisation. Valsartan forms labile "solvate crystals" from ethyl acetate /cyclohexane, the solvent for final purification. During the drying process the microscopically visible solvate crystals decay to the very fine particle size of the active substance and the crystalline properties are mainly lost rendering a poorly crystalline material.
Alternative processes for some intermediate compounds, which are maybe employed in all sites registered to manufacture these compounds, always lead to active substance of equivalent quality.
Valsartan is manufactured via a synthetic route introduced years ago. All starting materials are commercially available and are well established, and controlled by adequate specifications.

- Specification

Valsartan specification includes tests for appearance (visual examination), absorbance (420 nm) and clarity of the solution in methanol, particle size (laser light diffraction), identity (IR, HPLC), R-enantiomer (HPLC), assay based on anhydrous and solvent-free substance (HPLC, titration), residual solvents (GC), related substances (HPLC), water content (KF), sulphated ash, heavy metals (X-ray fluorescence) 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 and is not susceptible to degradation even when stored at elevated conditions of temperature and humidity. All batches comply with the proposed specification at all storage conditions. A retest period of 3 years without special requirements for storage is acceptable.

Medicinal Product

- Pharmaceutical Development

The aim of formulation development was an immediate release tablet combination product that would be bioequivalent to the marketed products containing each substance individually.
The development of Exforge was highly based upon the formulation and manufacturing process of the already authorised valsartan and valsartan /hydrochlorothiazide film-coated tablets, because of the applicant's extensive knowledge of these formulations.
Four formulations have been developed 2.5/80, 5/80, 5/160 and 10/160. The 5/80 and 5/160 mg formulations, are weight and dose proportional to 10/160 and 2.5/80 mg respectively. The 2.5/80 mg formulation has not been applied for in the present application, but was only used for formulation development
A compatibility study was conducted using marketed valsartan and amlodipine film-coated tablets, which had been ground and mixed. Results from this study demonstrated no significant degradation. Stability data confirm these findings.
The influence of the particle size of both APIs on blend homogeneity and processability has been studied and additional requirements for particle size for both substances have been setThe choice and function of the excipients in the formulation has been adequately described. The compatibility of the active substances with the excipients has been confirmed. No organic solvents are used for the coating suspension. All the excipients comply with pharmacopoeial standards. The tablet film-coating colour formulation is a non-functional coating used for colour differentiation and masking the slightly bitter taste of valsartan.

Two bioequivalence studies have been performed. One study compared the 2.5/80 mg film-coated tablets to marketed valsartan 80 mg capsules and amlodipine encapsulated 2.5 mg tablets. The second study compared the 10/160 mg film-coated tablets to marketed valsartan 160 mg capsules and 2 amlodipine 5 mg over-encapsulated tablets. Comparative dissolution profiles between marketed valsartan capsules, encapsulated amlodipine besilate tablets and the respective strengths of Exforge tablets used in the bioequivalence studies were shown to be comparable.
The composition of the batches used for BE studies is identical to the final product except for the coating. The tablet film-coating color formulations were further optimized for colour differentiation.
Since 2.5/80 and 10/160 mg formulation were found to meet the bioequivalence criteria, the development of these dosage strengths advanced without further modification.
As far as the 5/80 and 5/160 mg formulations are concerned, these are weight and dose proportional to 10/160 and 2.5/80 mg formulations. In addition dissolution profiles in three different media (pH 6.8, 4.5 and 1.0, Ph.Eur. Apparatus II (paddle)) are provided comparing 5/80 mg to 10/160 mg film coated tablets and 2.5/80 mg to 5/160 mg film coated tablets. The similarity factor f_2 was calculated for each combination of tablets. In all media and for both active substances the similarity factor f_2 was between 50 and 100 as required by the EU guideline CPMP/EWP/QWP/1401/98. Furthermore, comparative dissolution profiles were presented between batches manufactured with amlodipine obtained from each of the two suppliers. Similar dissolution profiles were seen with amlodipine from the two suppliers; in all cases the similarity factor f_2 was within between 50 and 100 suggesting similarity. Moreover, the manufacturing process of the two products is identical and valsartan and amlodipine exhibit linear and dose proportional pharmacokinetics. This rationale is in line with the criteria set in the NfG on the Investigation of Bioavailability and Bioequivalence and based on appropriate data provided a bioequivalence surrogate inference for the 5/80 and 5/160 mg strengths was endorsed.

- Adventitious Agents

None of the excipients are of animal or human origin.

- Manufacture of the Product

A standard dry granulation technique is employed, comprising the following steps: pre-blending and screening, second blending, compaction and screening, of final blend and compression and, finally, 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 includes tests for: appearance (visual examination), identification of amlodipine and valsartan (TLC, HPLC), identification of colourants (colour reaction), mean tablet mass, dissolution (HPLC, UV), degradation products of amlodipine (HPLC); assay for valsartan and amlodipine (HPLC), uniformity of dosage units (Ph. Eur), and Microbial limit tests.
The specification has been established after analyzing pilot and commercial size batches for all strengths manufactured with amlodipine obtained from both sources. The results comply with the specification and confirm consistency of the product.

- Stability of the Product

12-months long-term and accelerated stability data of 3 batches (1 production and 2 pilot scale batches) of each strength in PVC/PVDC (DPX) blister package have been provided.
These batches have been stored for 12 months at 25 ºC /60 % RH and at 30 ºC /70 % RH, respectively 30 °C/75% RH and at 40 ºC /75 % RH for 6 months in the proposed market packaging. The testing at 25 ºC /60 % RH and at 30 ºC /75 % RH will continue for 36 months.
Parameters investigated: Appearance (visual examination), water content (KF), dissolution for amlodipine and valsartan (HPLC), assay and related substances for amlodipine and valsartan (HPLC) and microbial limits testing.
As expected, results for Exforge film-coated tablets stored in DPX blisters fail to meet specifications for assay, related substances and dissolution when stored at the accelerated storage conditions, but comply with the specifications after 12 months on stability under the intermediate storage condition of 30 °C /65 % RH as well as under normal conditions.
In addition, one batch of each strength stored at -20 °C for 6 months and at 50 °C for 3 months remained stable.
Finally, one batch of each strength was tested at 1.2×10^6 lux hours and 200 watt/m^2 and the product was shown to be photostable.
On the basis of the provided data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and medicinal product has 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 CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

3. Non-clinical aspects

After registration of valsartan, no further *in vivo* preclinical safety, ADME and pharmacokinetics studies were performed. However, recent mechanistic studies on CYP interaction and the elimination mechanism have been published. Minimal information on the preclinical safety and pharmacokinetics of valsartan was provided to support this application, with a focus on newer mechanistic data.

The preclinical safety, preclinical pharmacokinetics and clinical pharmacokinetics information of amlodipine have been presented in numerous publications. The preclinical safety, ADME or pharmacokinetics studies with amlodipine alone were not performed, except for a rising-dose study in marmosets. Published information on the preclinical safety, ADME and pharmacokinetics of amlodipine was the basis for the assessment. In particular, preclinical and clinical drug interaction data

on amlodipine were evaluated. Based on the available data on valsartan and amlodipine, the potential for interaction between valsartan and amlodipine, and potential interactions of FCP with other drugs was assessed.

In line with the *Draft Guideline on the non-clinical development of fixed combinations of medicinal products (CHMP/SWP/258498/2005*), the Applicant has performed also an abridged toxicological evaluation of the fixed combination of valsartan and amlodipine (VAA489), comprising 3-months repeat dose toxicity studies in the rat and marmoset and an embryo-fœtal development study in the rat.

Pharmacology

- Primary pharmacodynamics

There are two experiments described demonstrating that a combined chronic oral treatment with valsartan and amlodipine produced additive blood pressure lowering effects in experimental models of hypertension. First refers to the chronic effects of combination therapy using valsartan and amlodipine on blood pressure, heart rate and cardiac mass were evaluated in the SHR (spontaneous hypertensive rats). In this study, valsartan and amlodipine were administered in drinking water either alone or in combination, and blood pressure and heart rate was recorded continuously using radiotelemetry for 6 weeks. Treatment with valsartan at a dose of 20 mg/kg/day or amlodipine at 8 mg/kg/day produced a 14-mmHg decrease in blood pressure. A similar blood pressure lowering effect was also achieved when the animals were treated with a combination of valsartan and amlodipine at 10 and 4 mg/kg/day, respectively. The combination treatment was found to significantly ($p < 0.05$) regress aortic hypertrophy ratios (vehicle control, 13.9 ± 0.5; combination treatment, 11.4 ± 0.2; $n \geq 13$) and left ventricular hypertrophy as determined by wet weight measurements (vehicle, 2.74 ± 0.11; combination treatment, 2.21 ± 0.02; normalized to body weight) in SHR upon sacrifice at the end of experiment. These results demonstrate that combined chronic treatment with valsartan and amlodipine elicited an additive decrease in blood pressure as well as beneficial effects on vascular hypertrophy and cardiac mass in this animal model of hypertension. In second experiment the effects of chronic treatment with valsartan, administered alone or in combination with amlodipine, on blood pressure and the progression of renal disease were investigated in SHRs injected with streptozotocin to induce diabetes. Valsartan and amlodipine were given by daily gavage for 32 weeks, and blood pressure was monitored by both tail-cuff plethysmography as well as radiotelemetry. Diabetic SHRs treated with valsartan at a dose of 30 mg/kg/day significantly reduced systolic blood pressure as assessed by radiotelemetry (vehicle control, 153 ± 6 mmHg; valsartan-treated, 135 ± 3 mmHg; mean ± SEM, n = 12). Similar results were obtained upon treatment with amlodipine at a dose of 6 mg/kg/day or the combination of valsartan and amlodipine at doses of 20 and 4 mg/kg/day, respectively, (129 ± 4 mmHg). Likewise, the three regimens also produced equihypotensive effects upon measurement by tail-cuff plethysmography. Thus, these results suggest that combined chronic treatment with valsartan and amlodipine produced an additional blood pressure lowering effects when compared to treatment with either drug alone. However, unlike valsartan mono-therapy that showed significant reductions in albuminuria (↓ 50%) and glomerulosclerosis, no renoprotective effects were observed in diabetic SHRs treated with an equihypotensive regimen of combination therapy using valsartan and amlodipine. The authors conclude that blood pressure reduction by itself is not an adequate predictor of subsequent renoprotection and that higher doses of agents which block the renin-angiotensin system may be required to optimize the beneficial renal outcomes in diabetes. In the opinion of CHMP, the two above-referenced studies in the SHR model sufficiently demonstrated additive lowering effect on blood pressure. The SHR is a state-of-the-art model of hypertension.

- Secondary pharmacodynamics

No new studies with FCP were conducted. In patients with hypertension not controlled by valsartan alone, treatment with a free combination of amlodipine and valsartan has been shown to be well-tolerated, safe, and efficacious (Stergiou et al., J Hypertension, 2005; 23:883-889). Furthermore, in clinical pharmacokinetics studies with the valsartan/amlodipine combination (VAC), no significant pharmacokinetic interactions were observed between amlodipine and valsartan. Valsartan does not inhibit CYP450 activities to any significant extent and is mainly eliminated by biliary excretion of unchanged drug, whereas, amlodipine is cleared metabolically. There was no interaction between

valsartan and amlodipine, and the combined data on amlodipine, valsartan and VAC indicated a rather low potential for interactions between VAC and co-medications. These results clearly indicate that the amlodipine/valsartan combination is safe and does not cause drug-drug interaction in human, a species that the drug is targeted to. Therefore, non-clinical pharmacology studies including secondary pharmacodynamics that concern non-selective interactions with off-targets and pharmacodynamic drug interaction were not conducted with VAC in animal species as these two drugs are currently being used in the medical practice as free combination.

- Safety pharmacology programme

No new studies with VAC were conducted. The non-clinical primary pharmacodynamics of VAC focus on the blood pressure-lowering effects through interactions of these two agents with angiotensin receptor type 1 and calcium channel, and they were documented in the application. These interactions are considered to be very specific by the general scientific community. For valsartan monotherapy, it has been clearly shown that this drug does not interact with calcium channel and a variety of other targets involved in the regulation of blood pressure. Likewise, amlodipine has also demonstrated a safe profile when given alone or in fixed-dose combination with benazepril (Faulkner and Hilleman, Exp Opin Pharmacother, 2001; 2:165- 178). Thus, the combination of amlodipine and valsartan is not expected to display concerns in safety pharmacology assays *in vitro*. For these reasons, non-clinical safety pharmacology for amlodipine/valsartan combination was not conducted.

- Pharmacodynamic drug interactions

No preclinical studies have been conducted to investigate any potential pharmacodynamic drug interactions between valsartan and amlodipine or between the combination drug and other drugs. Additive action was observed.

Pharmacokinetics

- **Pharmacokinetic studies**

Valsartan

In the rat, marmoset and human, valsartan was absorbed to a moderate extent. Exposure to valsartan increased dose-dependently and partly dose-proportionally. Valsartan was metabolized to a minor degree. Its elimination was largely mediated by biliary excretion of unchanged drug. Hepatobiliary elimination appears to be due partly to MRP2, but other transporters may contribute as well. Valsartan did not inhibit CYP activities to any significant extent, and is highly unlikely to alter the CYP-mediated metabolic clearance of co-medications. Conversely, CYP inhibitors or inducers are unlikely to alter the clearance of valsartan. The drug interaction potential of valsartan has been shown to be very low.

Amlodipine

Amlodipine was well absorbed in animals and in humans following oral administration. Oral bioavailability in humans was 64%, and was 88-100% in rats, dogs and mice. Plasma clearance of amlodipine in human was low (7 mL/min/kg), the volume of distribution was large (21 L/kg), and the terminal half-life was long (34 h). The pharmacokinetics of amlodipine in humans was linear. In all species, amlodipine was extensively metabolized to inactive metabolites, which were excreted via both the renal and biliary routes. The primary metabolic pathway of amlodipine involved oxidation of the dihydropyridine ring. Subsequent oxidation steps lead to a variety of metabolites. Plasma protein binding of amlodipine in humans was 98%. Amlodipine was mainly but slowly eliminated through CYP3A-mediated metabolism. Therefore it may interact potentially with potent CYP3A inhibitors or inducers. Decreased clearance of amlodipine has been reported in clinical drug interaction studies with strong CYP3A inhibitors. Amlodipine showed a moderate to low potential to inhibit CYP1A1 and CYP2B6-mediated metabolic drug clearance. These enzymes, however, appear to play very limited roles in the elimination of drugs.

Valsartan/amlodipine

Toxicokinetics studies in rat and marmoset demonstrated dose-dependent or dose-proportional exposure to both drugs. At NOAEL, the exposure to both drugs (AUC, C_{max}) was mostly larger than the human exposure, with exposure multiples ranging from 0.3 to 32.5. The data show a moderate safety margin for humans. No pharmacokinetic interaction between valsartan and amlodipine was observed in toxicokinetics studies. The potential for interactions of VAA489 with co-medications is

considered as low. However, very strong inhibitors of CYP3A may increase the exposure to amlodipine.

- **Methods of analysis**

In toxicokinetics studies, the concentrations of valsartan and amlodipine were determined in plasma by specific, validated HPLC-MS/MS methods. The lower limits of quantification were 200, 20 or 5 ng/mL for valsartan and 5, 1 or 0.375 ng/mL for amlodipine. The analytical methods were suitable for analysis of plasma concentrations in the toxicity studies. References are given in the dossier.

- **Absorption**

Valsartan

In the rat valsartan was absorbed to a moderate extent (41%). The extent of absorption in marmoset and human was similar, but is not exactly known. Exposure to valsartan increased dose-dependently and partly dose-proportionally.

Amlodipine

Oral doses of amlodipine 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 amlodipine, appearance of amlodipine and total drug-related material in the plasma was gradual with peak concentrations attained around 6-9 h. Unlike verapamil, diltiazem and nifedipine, amlodipine did not undergo extensive and variable presystemic metabolism. 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 amlodipine in humans. Activated charcoal almost completely prevented amlodipine absorption when administered immediately after amlodipine ingestion, and reduced absorption by 49% and 15% when administered with a delay of 2 h and 6 h, respectively. This could be the method of choice to prevent absorption in amlodipine overdose.

- **Distribution**

Valsartan

Valsartan was highly bound to proteins of plasma or serum. The drug proportion bound, determined by equilibrium dialysis, was 96% in humans, at drug concentrations up to 5 µg/mL. Valsartan was mainly bound to albumin (92%), and less to alpha 1-acid glycoprotein (22%). Binding to gamma globulins was negligible. Valsartan was not displaced by diclofenac, warfarin, furosemide, and hydrochlorothiazide. High binding was also seen in marmoset (95-96%), rats (96-98%), dogs (95-97%), rabbit (90-98%), while binding was lower in the mouse (75-89%).

Amlodipine

Amlodipine was highly distributed into tissues with a large volume of distribution around 21-32 L/kg across species. PET (positron emission tomography) analysis was carried out in dogs dosed ^{11}C-labeled amlodipine. The myocardial concentration increased after a bolus injection to reach a maximum in 2 min and then remained on a plateau with a slight downslide while the blood concentration fell relatively rapidly. Myocardial uptake was threefold higher than lung uptake. Amlodipine was highly bound to plasma protein and the percentage of drug bound was 98% in humans, 97% in dogs, and 94% in rats, at a drug concentration of 50 ng/mL (references are given in the non-clinical overview).

- **Metabolism**

Valsartan

Valsartan was poorly metabolized in animals and humans. In the marmoset, an inactive, hydroxylated metabolite was recovered in the excreta. In the rat a minor dose proportion underwent glucuronidation. In human, the same minor hydroxylated metabolite was found as that in the marmoset.

Amlodipine

Amlodipine was eliminated mainly through extensive, though slow metabolism, prior to excretion. Metabolism was similar in rats, dogs and mice. 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. Initial metabolism involved oxidation of the dihydropyridine ring of the racemic compound to the pyridine analogue in human, rat and dog. Further metabolism involved side-chain oxidation and hydrolysis of the side-chain ester(s). In dogs the major metabolites were formed by

oxidation of the aminoethoxymethyl side chain. In contrast, the major metabolites in the rat retained this side chain intact while the 5-methoxycarbonyl substituent was demethylated. In human, following oxidation to its pyridine derivative subsequent metabolism involved both routes found for the rat and the dog. Amlodipine was metabolized mainly by hepatic CYP3A, but slowly and with low first pass extraction.

- **Excretion**

Valsartan

Valsartan was excreted largely via bile and faeces, with 9% of the dose recovered in human urine only about a quarter of the absorbed dose (human). Recovery in urine was ≤16% of the dose in marmosets, and <2.5% of the dose in rats. The mechanism of the hepatobiliary elimination of valsartan, which is a di-anion at physiological pH, was investigated in normal and mrp2-deficient rats *in vivo* Tr-rat and EHBR rat. Valsartan elimination with bile depended to about 50% on the presence of canalicular mrp2 (cMOAT). Also, in canalicular plasma membrane vesicles in vitro, valsartan was shown to be a substrate of mrp2. Further, at least an additional ATP-dependent transporter, probably of the mrp family contributes to elimination. Valsartan did not interact with bile acid transport or with Pgp (mdr1). Using transfected cells, valsartan was shown to be a substrate of the hepatic uptake transporters OATP1B1 and OATP1B3.

Amlodipine

In rats, 33-38% of the dose was recovered in the urine and 58-60% in faeces. In both male and female dogs, 38-51% of the dose was 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. In healthy adult volunteers, following single 5 mg intravenous and 15 mg oral doses of 14C-labeled amlodipine in a crossover design, the amount of dose recovered was 59-62% in the urine and 23% in the faeces, within 12 days after dose administration. Mean total radioactivity recovery averaged 84%, but seemed to continue beyond 12 days. Studies *in vitro* suggested that amlodipine was a weak substrate of P-gp.

- **Pharmacokinetic drug interactions**

Valsartan

Valsartan was mainly cleared through biliary excretion, and the contribution of metabolism was minor. Therefore, the clearance of valsartan is unlikely to be altered by CYP inhibitors or inducers. 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. This concentration is beyond the therapeutic range and the theoretical potential to alter the CYP-dependent metabolic clearance of any co-medications is extremely low. In rats, based on studies *in vitro* and *in vivo* in wild-type and transport-deficient strains, the hepatobiliary elimination of valsartan depended to about 50% on the canalicular anion transporter mrp2, see above. Other transporters, probably of the mrp family, are likely to contribute to elimination. Valsartan did not interact with bile acid transport or P-gp (mdr1). Valsartan was shown to be a substrate of the hepatic uptake transporters OATP1B1 and OATP1B3. Clinical drug interaction studies with valsartan are described in the clinical section of this assessment report. Based on the preclinical and the available clinical findings with valsartan, the potential for clinical drug interactions with valsartan appears to be very low. The main elimination mechanism for valsartan in humans is likely to be hepatic canalicular transport by MRP2. According to the currently available literature on MRP2, apparently few clinically significant drug interactions via MRP2 have been reported. It should be noted that the knowledge on substrate specificities, regulation mechanisms, and inhibitors and inducers of MRP2, and of transporters in general, is still limited, and the predictivity of current *in vitro* or animal models and the thus obtained data is still uncertain.

Amlodipine

Amlodipine is eliminated mainly through metabolism by hepatic CYP3A. Potentially, co-medications might interact with amlodipine by inhibition or induction of CYP3A. Conversely, amlodipine might interact with co-medications, via CYP isoenzymes involved in their metabolism. In studies in vitro, among the human CYP isoforms evaluated (1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4), amlodipine 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

amlodipine following 10 mg once daily doses was around 0.062 μM (18.1 ng/mL), corresponding to I/Ki values of 0.5 and 0.03 for CYP1A1 and CYP2B6, respectively. These I/K_i values suggest a moderate to low potential of amlodipine to inhibit CYP1A1- and/or CYP2B6-mediated metabolic clearance. These two enzymes, however, appear to play very limited roles in the elimination of drugs. (References are given in the non-clinical overview) Grapefruit juice had at most a marginal effect on the pharmacokinetics of amlodipine when co-administered to humans. Cimetidine, telmisartan or benazepril, did not significantly alter the pharmacokinetics of amlodipine in patients when each was co-administered with amlodipine. Sildenafil, which is mainly metabolized by CYP3A, did not change amlodipine PK, nor was any synergistic blood pressure lowering observed. Indomethacin had no effect on blood pressure in amlodipine treated patients. When potent CYP3A inhibitors, such as diltiazem, were co-administered to humans with amlodipine, plasma C_{max} and AUC of amlodipine increased by up to 57%. The combined HIV protease inhibitors indinavir and ritonavir, very strong inhibitors of CYP3A, increased the AUC of amlodipine by 90%. Increased response to amlodipine appears likely, and the amlodipine dose should be titrated to response and side effects. Clinical literature data show few interactions of amlodipine with co-medications. Amlodipine did not affect the pharmacokinetics of cardiovascular drugs digoxin, telmisartan, nor benazepril. Amlodipine increased AUC and C_{max} of the hypocholesteremic drug simvastatin by 28% and 43%, respectively, though without an effect on cholesterol. It caused none to minor increase of cyclosporine A plasma levels. Amlodipine had no effect on the PK of the HIV protease inhibitors. There are no clinical data indicating CYP induction by amlodipine, which would result in interaction with co-medications. In a mechanistic study in the mouse, amlodipine had no effect on the PK of antiepileptics. Though amlodipine reduced pentylenetetrazole-induced seizures, enhancing the protective effect of antiepileptics valproic acid, phenobarbital and ethosuximide. Due to the potential pharmacodynamic interaction, the authors did not recommend combination of amlodipine with antiepileptics. In vitro studies using human plasma showed that amlodipine did not alter the protein binding of commonly used drugs such as warfarin, phenytoin, digoxin, or indomethacin. In studies in vitro, amlodipine was a substrate of P-gp, and was concluded to be a class I modulator of P-gp. At amlodipine concentrations <3 μmol/L, no effect on P-gp was found. At higher amlodipine levels, stimulation of P-gp was seen, and inhibition was observed at 20 μmol/L. Amlodipine did not inhibit the P-gp-mediated transport of digoxin in vitro, and moderately inhibited the transport of daunorubicin with a K_i value of 22 μM. The clinical significance of the in vitro findings remains to be further assessed. In kidney transplant patients, amlodipine increased the AUC0-2h of cyclosporine by 16%.

Valsartan/amlodipine

In toxicokinetics studies with the combination of valsartan and amlodipine, no relevant pharmacokinetic differences were found from the pharmacokinetics of the individual drugs when administered alone. Thus no obvious interaction between the two drugs was observed. Clinical pharmacokinetics studies with VAA489 are discussed in the Clinical Overview. There was no significant pharmacokinetic interaction between amlodipine and valsartan. The combined data on amlodipine, valsartan and VAA489 indicate a rather low potential for interactions between VAA489 and co-medications. Relevant pharmacokinetic interactions may occur only with strong inhibitors of CYP3A enzymes. However, even in case significant pharmacokinetic interactions are found, the interaction may not necessarily be clinically relevant. No specific studies of drug interaction were conducted. In patients with hypertension not controlled by valsartan alone, treatment with a free combination of amlodipine and valsartan has been shown to be well-tolerated, safe, and efficacious (Stergiou et al., J Hypertension, 2005; 23:883-889). Furthermore, in the response to Preclinical safety studies below, it is stated, "In clinical pharmacokinetics studies with the VAA489 combination, no significant pharmacokinetic interactions were observed between amlodipine and valsartan. Valsartan does not inhibit CYP450 activities to any significant extent and is mainly eliminated by biliary excretion of unchanged drug (via hepatobiliary anion transporters, mainly MRP2); whereas, amlodipine is cleared metabolically. There was no interaction between valsartan and amlodipine, and the combined data on amlodipine, valsartan and VAA489 indicate a rather low potential for interactions between VAA489 and co-medications." These results clearly indicate that the amlodipine/valsartan combination is safe and does not cause drug-drug interaction in human, a species that the drug is targeted to. Therefore, non-clinical pharmacology studies including secondary pharmacodynamics that concern non-selective interactions with off-targets, and pharmacodynamic drug interaction were not conducted with fixed dose combination of amlodipine/valsartan in animal species as these two drugs are currently being used in the medical practice as free combination.

Relevant data pertinent to monotherapy of valsartan were submitted along with the original submission of valsartan and the data pertinent to amlodipine is available in literature and public domains.

- **Other pharmacokinetic studies**

Valsartan

The pharmacokinetics of valsartan has been presented in detail in the NDA.

Amlodipine

Rats showed higher plasma clearance (122 mL/min/kg) than human (7 ± 1.3 h mL/min/kg), dog (11 mL/min/kg), and mouse (28 mL/min/kg). Consequently, the terminal half-life of amlodipine in plasma was shorter in rat (3 h) than in human (34 ± 5 h), dog (30 h), and mouse (11 h). Following oral administration, maximal plasma concentration of amlodipine was achieved around 3 h in rats, and around 6-9 h in human, dog, and mouse, consistent with the higher clearance in the rat. The pharmacokinetics in the marmoset after single dose was not investigated. In healthy male volunteers, a linear relationship of AUC and C_{max} to dose was observed following single oral doses of 2.5, 5, and 10 mg. Steady-state plasma amlodipine concentrations were obtained after about 7 days of oral 10 mg once-daily administration. The C_{max} at day 14 was 18.1 ± 7.1 ng/mL compared with 5.9 ± 1.2 ng/mL after a single dose. Plasma amlodipine trough-to-peak ratios were 0.67±0.08 at steady state. In young patients with hypertension, the clearance of amlodipine was comparable with that in young normotensives. Renal insufficiency had no significant impact on the disposition of amlodipine. The pharmacokinetic properties of amlodipine were comparable in diabetic (with T2DM) and nondiabetic hypertensive patients. The pharmacokinetic properties (AUC, C_{max}, and trough levels) were similar in healthy subjects with slow (>35 h) or rapid (<15 h) GI transit. In elderly hypertensive patients, the half-life of amlodipine was somewhat longer than in young volunteers (64 ± 20 vs. 48 ± 8 h). This was associated with somewhat decreased clearance (309 ± 90 vs. 410 ± 134 mL/min) in the elderly. Patients with hepatic cirrhosis showed longer half-life (60 h) than healthy volunteers (34 h). In addition, AUC tended to be greater in the patients with cirrhosis (166 vs. 118 ng*h/mL) although the difference did not attain statistical significance. Relevant dose regime adjustment in both the elderly and patient with hepatic cirrhosis may be necessary in light of the pharmacokinetic behaviour of amlodipine in these two groups. The pharmacokinetics of R-(+)- and S-(-)-amlodipine after single enantiomer administration were comparable to that of each enantiomer after administration of the racemate. No racemisation occurred *in vivo* in human plasma.

Valsartan/amlodipine

For VAC product, based on the established properties of both drugs, no relevant pharmacokinetic interaction, and no change in their general disposition were expected. The nonclinical pharmacokinetics program was limited to toxicokinetics studies, which included drug components, valsartan and amlodipine, as part of the toxicity testing of the combination drug in rat and marmoset. CHMP is of the opinion that the pharmacokinetics of each of the individual compounds has been sufficiently described; and, as based on the toxicokinetics studies of the combination, no significant impact on individual pharmacokinetics may be anticipated with valsartan/amlodipine FCP.

Toxicology

- Single dose toxicity

No studies conducted with the VAC product and in the opinion of the CHMP the justification provided by Aplicant is sufficient.

- Repeat dose toxicity (with toxicokinetics)

With the combination product, toxicity studies were performed in rat and marmoset. Concomitant toxicokinetics studies were performed to demonstrate adequate exposure of the toxicity test animals, as well as to characterize the pharmacokinetics of the two drugs in combination treatment. Toxicity studies were performed with VAC product in rat and marmoset and included dose range-finding studies in rat and marmoset, 13-week GLP-studies in rats and marmosets and an embryo-foetal developmental GLP-study in rats. This preclinical safety program was approved earlier by the FDA and is consistent with the FDA Guidance from January 2005 as well as the *CHMP Draft Guideline on the nonclinical safety evaluation of FCP*. Based on the doses of valsartan and amlodipine in the

clinical trials for this combination, a ratio of 16:1 (valsartan: amlodipine on a weight basis) was used in these preclinical safety studies. All animals were dosed orally by gavage. VAC product was generally well tolerated and no toxicities were identified that would be prohibitive for use in humans. The rat and marmoset were selected as the rodent and non-rodent species because these species, respectively, are used routinely in toxicity evaluations and both were used during the development of valsartan. In preclinical safety studies, VAC was associated with changes in the kidney, erythrocyte parameters, gastrointestinal tract, heart and adrenals and each of these effects could be attributed to known effects of one or both components, often due to exaggerated pharmacological effects. Of these effects, nephropathy, medial hypertrophy of renal cortical arterioles, decrease in erythrocytic parameters and decreases in heart weight were associated with valsartan administration. Increases in erythrocytic parameters, ulcers in the oesophagus, nonglandular stomach and large intestine, inflammation in the right atrium of heart and adrenal cortical hypertrophy were associated with amlodipine administration. Erosions/ulcers in the glandular stomach and small intestines and adrenal cortical vacuolation were associated with valsartan and/or amlodipine administration. Since these changes were associated with valsartan and/or amlodipine, it should not be of major concern because both these drugs have been used safely in the clinics for a long time as monotherapies as well as in free combinations. Overall, FCP was generally well tolerated by rats and marmosets in general toxicity studies and no toxicities were identified that would prohibit its use in humans. Since most of the target organ toxicities are monitorable and were associated with exaggerated pharmacological effects of valsartan and/or amlodipine, none should be of major concern. Moreover, both these drugs have been used in the market safely for a very long time and have often been used concomitantly. CHMP is of the opinion that the toxicological findings can be monitored in the clinical settings and labelled in the SPC.

Toxicokinetics of VAC was investigated in the 13-week rat toxicity study. Based on dose normalized AUC0-24h values, exposure was under proportional at higher dose levels. No tendency for accumulation was detected between day 1/2 and 64/65. Amlodipine had no effect on valsartan exposure. However, on day 64/65 the C_{max} in females was higher when valsartan was administered alone than that when administered in combination with amlodipine (133 versus 19.7 µg/mL). Maximal plasma concentrations of amlodipine were observed between 0.5 and 6 h after administration. In some cases, the exposure to amlodipine was lower in males compared to females. On day 1, AUC0-24h-based exposure to amlodipine, among the three combination doses, appeared to increase less than dose proportionally in male and female rats. By contrast, on Week 10, the exposure to amlodipine, among the three combination doses, appeared to increase more than dose proportionally in males whereas the increase was quite dose proportionally in females. AUC0-24h-based exposure to amlodipine was higher at Week 10 compared to Day 1. On Day 1, AUC0-24h-based exposure to amlodipine was lower after dosing with the high combination compared to the high dose of amlodipine alone in males and females.

Toxicokinetics of VAC was investigated also in the 13-week marmoset toxicity study. In this study valsartan was rapidly absorbed with a t_{max} between 1 and 3 h. C_{max} for valsartan increased proportionally with dose. The C_{max} data showed considerable variability. Exposure increased proportionally with increasing dose. There was no consistent difference in exposure between males and females. There was no accumulation seen with repeated dosing except for the males in the 40:2.5 mg/kg/day group. However there was only one animal in this group. The valsartan concentrations in the 160/10/80/5 and 160/0/80/10 groups were similar, suggesting no effect of amlodipine on valsartan absorption and deposition. Samples from the control group animals did not have any measurable concentrations of amlodipine. Amlodipine concentrations peaked between 3 and 8 h. It appears there is a dose related increase in C_{max} with a considerable variability. Likewise, the exposure of amlodipine (AUC) also shows a dose-related increase. With a limited number of animals, there were gender differences in C_{max} and AUC. There was no accumulation with repeated dosing; however it is important to note that the dose at the higher dosage levels was halved during the study. In marmosets, it may be concluded that: marmosets in all test-article treated dose groups were exposed to valsartan and amlodipine, the exposure to valsartan increased proportionally with increasing dose, and exposure to amlodipine increased with increasing dose, no consistent difference in exposure to valsartan was observed for male and female marmosets (some differences in exposure to amlodipine were observed for male and female marmosets), exposure was generally similar following single and multiple doses for valsartan and amlodipine, and the concomitant administration of amlodipine had no effect on the

exposure to valsartan. There were not observed any unexpected interactions with the combination within an adequate range of concentrations and exposures in rat and marmoset monkeys given VAA489 or amlodipine/valsartan separately for up to 13-weeks. Considerations given in *CHMP guideline for the nonclinical development of fixed combinations (CHMP/EMEA/CHMP/SWP/258498/2005)* have been adequately addressed.

- Genotoxicity

No studies were conducted with the combination. Genotoxicity studies have been performed with amlodipine and valsartan, separately.

- Carcinogenicity

No studies were conducted with the combination. Carcinogenicity studies have been performed with amlodipine and valsartan, separately.

- Reproduction Toxicity

In an embryo-foetal development study in rats, VAC was not teratogenic. VAC at 160:10 mg/kg/day and amlodipine at 20 mg/kg/day showed maternal toxicity but had no effects on the developing embryo-foetus. At 320:20 mg/kg/day VAC and 320 mg/kg/day valsartan, there was an increased incidence of dilated ureters. At 320:20 mg/kg/day VAC, foetal skeletal findings of misshapen sternebrae and un-ossified forepaw phalanges were noted, which were considered to be an indication of developmental delays noted in the presence of significant maternal toxicity. In conclusion, treatment-related maternal and foetal effects were noted at the high dose combination of 320:20 mg/kg/day. Amlodipine alone at 20 mg/kg/day and VAC at 160:10 mg/kg/day produced evidence of maternal toxicity but had no effect on the developing embryo/foetus. The maternal NOAEL for VAC was 80:5 mg/kg/day while the embryo/foetal NOAEL was 160:10 mg/kg/day. No teratogenicity of valsartan/amlodipine was flagged in this study, and kinetics of the individual compounds was not significantly altered by the combination treatment. For evaluation of prenatal and postnatal development, including maternal function, the applicant refers to earlier studies with amlodipine and valsartan.

- Local tolerance

No studies were conducted.

Ecotoxicity/environmental risk assessment

An environmental risk assessment report has been submitted. The introduction of Exforge to the market is not likely to lead to a significant increase of neither amlodipine nor valsartan in the environment because patients receiving Exforge will typically discontinue treatment with monotherapies containing either amlodipine or valsartan alone, leading to a substitution of older monotherapy treatments with Exforge treatment. In accordance with the principles of the CHMP guideline (Doc. Ref. EMEA/CHMP/SWP/4447/00), significant increase in the extent of the use of amlodipine and valsartan will not be expected from the introduction of Exforge, and therefore an environmental risk assessment might not be needed at all. Nevertheless, the applicant has conducted a data-driven assessment that overall shows that there is no immediate concern for surface water, sewage treatment plants and for soil due to the use, storage and disposal of Exforge. The assessment discusses the potential concern for amlodipine transfer into sludge and subsequent soil, and points to the fact that concentrations is expected to be many-fold lower of what could be cause for concern. The CHMP considers the applicant's assessment of potential environmental risks of Exforge acceptable, and agrees to the conclusions of the ERA report.

4. Clinical aspects

Introduction

Despite the availability of many newer antihypertensive agents, hypertensive patients remain at higher risk of premature death than the general population. This persistence of morbidity and mortality may be accounted for by the frequent failure to achieve adequate blood pressure reduction despite an extensive array of available antihypertensive agents. Such considerations have led to reassessment of the potential role of FCP agents in the antihypertensive armamentarium. The rationale for combination therapy relates to the concept that antihypertensive efficacy may be enhanced when two classes of agents are combined. In addition, combination therapy may enhance tolerability. FCP therapy simplifies the treatment regimen, may prevent treatment failures that might result from missed doses. Development of an ARB/CCB combination product is based on an increasing need for effective treatment of HTN. The combination of valsartan and amlodipine is chosen due to their pharmacological properties including clinical effectiveness and lack of pharmacokinetic interactions. This application concerns Exforge, film-coated tablets 5/80, 5/160 and 10/160 mg, which contain FCP of amlodipine besylate and valsartan as active substances. Amlodipine is a CCB on the market for treatment of HTN and angina pectoris. Valsartan is a selective angiotensin II (AT_1) receptor antagonist, approved for treatment of HTN and heart failure. Both substances have been approved as monotherapy for at least ten years and there is some clinical experience of their use in non-fixed combination. The indication granted for Exforge is treatment of essential HTN in patients whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

The clinical development program for valsartan/amlodipine fixed combination products included the bioequivalence studies and phase III clinical efficacy/safety studies. In line with the guidance documents (*Note for Guidance on Fixed Combination Medicinal Products, CPMP/EWP/240/95; Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, CPMP/EWP/238/95 Rev. 2*) it consisted of placebo and active controlled studies (factorial design and non-responder) performed in order to justify the second line use of the fixed combination and the proposed dosages. Bioequivalence data have been provided to bridge from the trial formulations to the intended commercial formulation. In addition, the Applicant's clinical summary contained a brief overview of pharmacokinetic and pharmacodynamic data of amlodipine and valsartan based on published and previously submitted data, respectively. The Applicant has submitted also a single-dose pharmacokinetic interaction study report concerning the two components.

GCP

The applicant states in the summary that all human studies in this program were conducted in accordance with Good Clinical Practices (GCP), with full ethics committee reviews and informed consent for all research subjects. The assessment of the clinical documentations did not raise concerns about compliance with GCP..

Pharmacokinetics

- Absorption

The following information from respective SPCs is available for both compounds administered separately. After oral administration peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion. Following oral administration peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%. This reduction in AUC is not accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

- Distribution

Data regarding distribution of amlodipine and valsartan have been derived from the SPC of both compounds administered in monotherapy and have not been re-assessed. Volume of distribution of amlodipine is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins. The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

- Elimination

No new studies have been performed. The following information from respective SmPCs is available for both compounds administered separately. Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites. Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. 10% of original amlodipine and 60% of amlodipine metabolites are excreted in urine. Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive. Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

- Dose proportionality and time dependencies

Dose proportionality of the FCP was not specifically assessed. According to the prescribing information of valsartan and amlodipine, both compounds possess linear pharmacokinetics. Dose normalised PK parameters and respective ratio of these parameters were calculated in a pilot BE study (Study A2302) where bioavailability of 80/2.5 mg FCP was compared to a free combination of 160 mg valsartan and 10 mg amlodipine. Pharmacokinetics of valsartan and amlodipine was dose proportional in doses of 80-160 mg and 2.5-10 mg, respectively.

- Special populations

No new studies have been performed with the FCP. The following information from respective SPCs is available for both compounds administered separately.

– Impaired renal function

Amlodipine: the pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Amlodipine is not dialyzable. Valsartan: renal clearance of valsartan accounts for 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with mild renal impairment (creatinine clearance 20-50 ml/min). Limited data are available in patients with moderate-severe impairment of renal function and a starting dose of 40 mg is recommended in these patients. No studies have been performed in patients undergoing dialysis. However, valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

– Impaired hepatic function

Amlodipine: patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC. Valsartan: on average, in patients with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan. Patients with severe hepatic impairment, cirrhosis, biliary obstruction are contra-indicated from using valsartan.

– Gender

Valsartan plasma concentrations were observed to be similar in males and females.

– Elderly

Amlodipine was equally well tolerated when used at similar doses in elderly or younger patients, normal dosage regimens are recommended.

A somewhat higher systemic exposure to valsartan was observed in some elderly subjects compared with young subjects. The applicant commits to examine if clinical data supports a dose reduction in the elderly patient population and if so the company should develop a new formulation with 40 mg valsartan.

– Children

No pharmacokinetic data of amlodipine and valsartan are available in the paediatric population.

- Pharmacokinetic interaction studies

Study 37 was a single dose, randomized, 3 period, crossover, study was performed to demonstrate the lack of pharmacokinetic interaction between valsartan and amlodipine. This study was submitted as a part of valsartan application. Critical evaluation of the study was performed during the assessment of valsartan and this study was not re-assessed in this application. The results from this study are reported in the SPC of the valsartan. Under section 4.5 (Interaction with other medicinal products) it is concluded that when used together with amlodipine no clinically significant change in the exposure of valsartan is expected. Amlodipine and valsartan have been used in medical practice as a free combination. Valsartan does not inhibit CYP450 activities to any significant extent and is mainly eliminated by biliary excretion of unchanged drug (mainly by MRP2). Amlodipine is cleared metabolically. Based on the literature data, amlodipine and valsartan do not inhibit CYP450 enzymes in vitro.

Clinical pharmacology development program

The results of the clinical pharmacology study programme consist of two pilot bioavailability studies and three definitive bioequivalence studies (see the table below). A bioequivalence development program was designed as part of the registration application. Based on the discussions with the EU health agencies, two definitive bioequivalence (BE) studies were conducted with the dose strengths, 80/2.5 mg and 160/10 mg valsartan/amlodipine. In addition, based on the compositional proportionality of active and inactive ingredients, and similarity in *in vitro* dissolution properties, biowaivers are being requested for the other two dose strengths, 80/5 mg and 160/5 mg of valsartan/amlodipine.

Study	Strength	Subjects	Aim of the study
Studies conducted as a part of this submission			
A2302	80/2.5 mg 160/10 mg	27	Pilot study, relative BA of FCP to free combination
A2303	80/2.5 mg	77	Pivotal study, BE between FCP and free combination
A2309	160/10 mg	68	Pivotal study, BE between FCP and free combination
37	160 mg 5 mg	12	Drug-drug interaction between amlodipine and valsartan
A2102	160/10 mg		BE between FCP and free combination of valsartan and EU-sourced amlodipine (pivotal BE studies A2303 and A2309 used US-sourced amlodipine encapsulated tablets in free combination arm) (ongoing)
A2313	160/10 mg		Food effect study

Study VAA489A2302 (Pilot Bioavailability)

CP-Study 2302 was an open-label, single-dose, three period, randomized crossover pilot study to investigate the relative bioavailability of 160/10 mg and 80/2.5 mg valsartan/amlodipine prototype

fixed combination tablet formulations compared to a free combination of marketed 160 mg valsartan and 10 mg amlodipine tablets. This was a pilot bioavailability study and was not powered to demonstrate strict bioequivalence. A total of 27 healthy male and female subjects were enrolled 25 subjects completed all study treatments and procedures. The dose adjusted C_{max} and $AUC_{(0-t)}$ of valsartan with the 80/2.5 mg fixed combination were comparable to that of the free combination of 160 mg valsartan and 10 mg amlodipine. The 90%CI of valsartan's C_{max} and AUC were within the bio-equivalence range of 0.8-1.25. On the other hand, the dose adjusted AUC_{0-t} of amlodipine with the 80/2.5 mg fixed combination was about 20% lower compared to the free combination of 160 mg valsartan and 10 mg amlodipine treatments, whereas the C_{max} was within the bio-equivalence range of 0.8-1.25. Since the comparisons were made between the dose-normalized data, the appeared differences in AUC could be attributed to in appropriate design of the study. Based on these results, the 160/10 mg and 80/2.5 mg fixed combination prototype tablets were scaled-up to bio-batch scale and used in the respective pivotal BE studies.

Study VAA489A2303 (Definitive Bioequivalence, 80/2.5 mg)

Study VAA489A2303 was an open-label, single-dose, two treatment, four period, replicate, randomized crossover study to demonstrate the bioequivalence between the fixed combination of valsartan/amlodipine 80/2.5 mg Final Market Image (FMI) tablet and the free combination of 80 mg valsartan and 2.5 mg amlodipine clinical service forms. Treatment A**:** Single dose of 80/2.5 mg fixed combination valsartan/amlodipine FMI tablet [Investigational] and Treatment B: Single dose of free combination of 80 mg valsartan (80 mg CSF) and 2.5 mg amlodipine (2.5 mg CSF) [Comparator]. Subjects were randomized to one of the two treatment sequences: ABAB or BABA. Seventy seven subjects were enrolled and 61 subjects completed all study requirements. PK parameters were plasma concentration vs. time-profiles used to determine AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{½}$, in all subjects for both Valsartan and amlodipine, using non-compartmental methods. The pharmacokinetic and statistical results indicate that the 90% confidence intervals for AUC_{0-t} and $AUC_{0-\infty}$ of valsartan were within the required acceptable bioequivalence range of 0.80-1.25, which indicates that the extent of absorption of valsartan between the fixed and free combination treatments is similar. The 90% confidence interval for C_{max} of valsartan was slightly outside the upper bound of the acceptable bioequivalence range while time to reach maximum concentration (T_{max}) was comparable. The point estimate and the corresponding 90% confidence interval of C_{max} were 1.17 and 1.06-1.29, respectively, which indicates that the mean rate of absorption as evidenced by C_{max} was 17% higher with fixed combination treatment compared to that of the free combination treatments. The point estimate falls within the established BE criteria of 0.80-1.25, while the upper limit of the confidence interval just outside the range. This minor deviation in C_{max} of valsartan with comparable exposure is considered not clinically relevant because valsartan is a chronically administered drug, has a wide therapeutic window of effect, and has an established safety profile in the dosage range of 20 to 320 mg. Furthermore, the 90% confidence intervals of amlodipine component for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} parameters were all within the established bioequivalence range of 0.80-1.25. These results indicate that the rate and extent of absorption of amlodipine from the fixed combination tablet are equivalent to those of the free combination treatment. In conclusion, with the exception of upper limit of the confidence interval for the C_{max} of valsartan, the FMI tablet containing 80 mg of valsartan and 2.5 mg of amlodipine met the bioequivalence criteria relative to the free combination of CSFs of 80 mg valsartan and 2.5 mg amlodipine capsules. Thus, the efficacy and safety data generated in phase III trials with the free combination of 80 mg of valsartan CSF and 2.5 mg amlodipine CSF can be extrapolated to the 80/2.5 mg valsartan/amlodipine fixed combination FMI tablet.

Study VAA489A2309 (Definitive Bioequivalence, 160/10 mg)

Study VAA489A2309 was an open-label, single-dose, two treatment, four period, replicate, randomized crossover study to demonstrate the bioequivalence between the fixed combination of valsartan/amlodipine 160/10 mg Final Market Image (FMI) tablet and the free combination of 160 mg valsartan and 10 mg amlodipine clinical service forms. Sixty eight subjects were enrolled and 54 subjects completed all study requirements. Each subject participated in a 21-day screening period, four baseline and treatment periods and an end-of study evaluation. An inter dose interval of at least 14 days was allowed between doses. During the four treatment periods the following two treatments were given twice under fasting conditions: treatment A (single dose of 160/10 mg fixed combination

valsartan/amlodipine FMI tablet [Investigational]) and treatment B (single dose of free combination of 160 mg valsartan (1 x 160 mg CSF) and 10 mg amlodipine (2 x 5 mg CSF) [Comparator]). Subjects were randomized to receive one of the two treatment sequences: ABAB or BABA. PK parameters were plasma concentration vs. time-profiles used to determine AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{½}$, in all subjects for both valsartan and amlodipine, using non-compartmental methods. The pharmacokinetic and statistical results indicate that the 90% confidence intervals for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of valsartan were within the required acceptable bioequivalence range of 0.80-1.25, which suggests that the rate and extent of absorption of valsartan between the fixed and free combination treatments are equivalent. Similarly, the 90% confidence intervals of amlodipine component for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} parameters were all within the acceptable bioequivalence range of 0.80-1.25. These results also indicate that the rate and extent of absorption of amlodipine between the fixed and free combination treatments are equivalent. In conclusion, the efficacy and safety data generated in phase III trials with the free combination of 160 mg of valsartan CSF and 10 mg amlodipine CSFs can be extrapolated to the 160/10 mg valsartan/amlodipine fixed combination FMI tablet.

Study VAA489A2102 (Definitive Bioequivalence, EU sourced amlodipine versus the FMI)
Study VAA489A2102 was an ongoing open-label, randomized, single-dose, two way cross over study to demonstrate the bioequivalence of amlodipine component between the fixed combination of 160/10 mg valsartan/amlodipine final market image (FMI) tablet and the 10 mg amlodipine tablet administered in combination with 160 mg valsartan clinical service form (CSF). Bioequivalence studies [CP-study 2303 and CP-study 2309] compared the fixed combination valsartan/amlodipine tablet against the free combination of clinical service forms (CSFs) of valsartan and amlodipine. The amlodipine CSF was an encapsulated US-sourced amlodipine tablet. The encapsulation was done to preserve the blinding. VAA489A2102 study specifically utilized EU-sourced amlodipine as the reference treatment to meet the registration requirements of the fixed combination valsartan/amlodipine tablet in the EU via the centralized procedure. Logarithmically transformed amlodipine PK parameters, AUC and C_{max}, were analyzed by a linear mixed effects model, with fixed effects for sequence, treatment and period and random effects for subject nested within sequence. The resulting 90% confidence intervals of the treatment mean ratios were used to evaluate the bioequivalence between the fixed combination (test) formulation and the free (reference) formulation. The rate (C_{max}) and extent (AUC) of absorption of amlodipine were equivalent between the 160/10 mg valsartan/amlodipine fixed combination final market image tablet and 10 mg EU-sourced amlodipine when administered in combination with 160 mg valsartan clinical service form thus the definitive bioequivalence of EU sourced amlodipine and the FMI has been demonstrated.

Study No. VAA489A37
The primary objective of the study was to determine whether a pharmacokinetic interaction exists between amlodipine and valsartan following single doses of 160 mg valsartan capsule, and 5 mg amlodipine tablet, alone and in combination, in healthy subjects. The study was a single-center, randomized, open-label, three-way crossover single dose trial in healthy subjects with a two week washout period between doses. Treatment A consisted of one 160 mg valsartan capsule administered orally as a single dose, treatment B – one 5 mg amlodipine tablet administered orally as a single dose and treatment C of one 160 mg capsule of valsartan and one 5 mg tablet of amlodipine administered orally together as a single dose, free combination. The duration of treatment was 10 weeks. Plasma concentration-time profiles were evaluated to determine the following pharmacokinetic parameters: AUC_{0-t}, the area under the curve from zero to the last sampling point; $AUC_{0-\infty}$, the area under the curve from zero to time infinity; C_{max}, the highest observed plasma concentration for each dose; and T_{max}, the time after each dose at which the highest observed plasma concentrated was reported. The parameters determined for valsartan and amlodipine administered as a free combination were compared to parameters determined for each drug administered alone. It was not the intent of this study to evaluate these results according to standard bioequivalence methodology, but rather to use these measures as a guide to interpretation of a pharmacokinetic interaction. The results of this study are presented in the table below. There was no pharmacokinetic interaction between amlodipine and valsartan. Therefore dosage adjustment of these medications when administered together should not be necessary.

Summary table for valsartan (t=48) and amlodipine (t=168) pharmacokinetic parameters: [Mean ±SD with % coefficient of variation: Tmax, given as median and range]

Treatment	AUC (0-t) (ng hr/ml)	AUC (0-∞) (ng hr/ml)	Cmax (ng hr/ml)
valsartan only (Treatment A)	17750 ± 8719 49% CV (N=12)	18063 ± 9775 54% CV (N=9)	2307 ± 1024 44% CV (N=12)
valsartan with amlodipine (Treatment C)	17993 ± 12228 68% CV (N=12)	19614 ± 14084 72% CV (N=9)	2269 ± 1571 69% CV (N=12)
90% Confidence Intervals for log-transformed values for ratio (C vs. A)	(0.81, 1.07)	(0.85, 1.17)	(0.69, 1.04)
amlodipine only (Treatment B)	189 ± 43.2 23% CV (N=12)	213 ± 54.4 26% CV (N=12)	3.37 ± 0.94 28% CV (N=12)
amlodipine with valsartan (Treatment C)	192 ± 43.0 22% CV (N=12)	226 ± 79.8 35% CV (N=12)	3.54 ± 0.65 19% CV (N=12)
90% Confidence Intervals for log-transformed values for ratio (C vs. B)	(0.96, 1.08)	(0.96, 1.14)	(0.98, 1.16)

Bio-waiver request for the 80mg/5 mg valsartan/amlodipine dose

This rationale is in line with the criteria set in the *Note for guidance on the investigation of Bioavailability and Bioequivalence*. The composition of 80/5 mg valsartan/amlodipine fixed combination FMI tablet is proportional in its active and inactive ingredients to the 160/10 mg valsartan/amlodipine fixed combination FMI tablet, for which the bio-equivalence has been established [CP-Study 2309]. In addition, the manufacturing process of the two products is identical. Furthermore, Valsartan and amlodipine exhibit linear and dose proportional pharmacokinetics. It has been demonstrated that *in vitro* dissolution of valsartan to and amlodipine to is comparable in three pH media between the 80/5 mg and 160/10 mg fixed combination products. In conclusion, the composition proportionality of the 160/10 mg and 80/5 mg valsartan/amlodipine fixed combination tablets, the same manufacturing process for these tablets, and the acceptable *in vitro* dissolution results fulfilled the requirements for both bioequivalence and bioequivalence waiver related to drug products that are proportionally similar in their active substance and excipients.

Bio-waiver request for the 160/5 mg valsartan/amlodipine dose

The request is based on the following rationale. This rationale is in line with the criteria set in the *Note for guidance on the investigation of Bioavailability and Bioequivalence*. The composition of 160/5 mg valsartan/amlodipine fixed combination FMI tablet is proportional in its active and inactive ingredients to the 80/2.5 mg valsartan/amlodipine fixed combination FMI tablet, for which the bio-equivalence was established [CP Study 2303]. In addition, the manufacturing process of the two products is identical. Furthermore, Valsartan and amlodipine exhibit linear and dose proportional pharmacokinetics. *In vitro* dissolution of valsartan to and amlodipine to is comparable in three pH media between the 160/5 mg and 80/2.5 mg fixed combination products; please refer to the figures below. In conclusion, the composition proportionality of the 80/2.5 mg and 160/5 mg valsartan/amlodipine fixed combination tablets, the same manufacturing process for these tablets, and the acceptable *in vitro* dissolution results fulfilled the requirements for both bioequivalence and bioequivalence waiver related to drug products that are proportionally similar in their active substance and excipients.

Influence of food

The effect of food on the oral bioavailability of single dose administration of 160/10 mg valsartan/amlodipine fixed combination tablet was investigated [Study 2313]. Food has no effect on the AUC of valsartan with slight decrease in C_{max} and T_{max} were observed. These slight changes in Cmax and Tmax are not considered clinically relevant. The rate (C_{max}) and extent (AUC) of absorption of amlodipine are comparable between fed and fasting conditions. In conclusion, the data suggest that the fixed combination tablets of valsartan/amlodipine can be administered without regards to meal.

Pharmacodynamics

Clinical pharmacology studies specifically designed to evaluate the pharmacodynamics of the fixed combination of valsartan/amlodipine were not performed. In the opinion of CHMP the combination may be safely administered as there is no pharmacokinetic interaction when the two drugs are co-administered.

Clinical efficacy

The targeted indication for Exforge is treatment of hypertension where monotherapy is not sufficient. Documentation of efficacy is based on 5 pivotal studies. Four of the pivotal studies, 2 double blind placebo controlled studies (A2201 and A2307), and 2 double-blind active controlled studies (A2305 and A2306) were performed in patients with mild to moderate essential hypertension, and 1 double-blind active controlled study (A2308) was performed in patients with severe hypertension. Long term data comes from 2 extension studies (A2201E and A2307E), results are dealt with under Clinical Safety. Two further studies (BR02 and study 21) are considered as supportive. The development programme is in compliance with current guidelines and obtained scientific advice from several national agencies.

The pivotal clinical studies are summarised below:

Study No.	Study objective	Patients randomized	Treatment duration	Treatment/dose (mg)	Efficacy endpoint
A2201	Efficacy and safety of various valsartan/ amlodipine combinations compared to their monotherapy components and to placebo, in patients with mild to moderate essential hypertension	1911	2-4 weeks 8 weeks	placebo run-in placebo valsartan 40 valsartan 80 valsartan 160 valsartan 320 amlodipine 2.5 amlodipine 5 valsartan/amlodipine 40/2.5 valsartan/amlodipine 40/5 valsartan/amlodipine 80/2.5 valsartan/amlodipine 80/5 valsartan/amlodipine 160/2.5 valsartan/amlodipine 160/5 valsartan/amlodipine 320/2.5 valsartan/amlodipine 320/5	Primary: change from baseline in MSDBP Secondary/other: change from baseline in MSSBP; standing SBP and DBP; sitting and standing pulse; responder rate; control rate
A2307	As for Study A2201	1250	2-4 weeks 8 weeks	placebo run-in placebo valsartan 160 valsartan 320 amlodipine 10 valsartan/amlodipine 160/10 valsartan/amlodipine 320/10	As for Study A2201

Study No.	Study objective, population	Patients randomized	Treatment duration	Dosage (mg)	Efficacy endpoint
A2305	Efficacy/safety of the combinations of valsartan/amlodipine 160/10 or 160/5 mg, compared to valsartan 160 mg alone in patients with essential hypertension not adequately controlled on valsartan 160 mg monotherapy	947	4 weeks 8 weeks	valsartan 160 run-in valsartan/amlodipine 160/10 valsartan/amlodipine 160/5 valsartan 160	Primary: MSDBP Secondary: MSSBP, responder rate, control rate, standing DBP and SBP, and sitting and standing pulse
A2306	Efficacy/safety of the combination of valsartan/amlodipine 160/10 mg compared to amlodipine 10 mg alone in patients with essential hypertension not adequately controlled on amlodipine 10 mg monotherapy	944	4 weeks 8 weeks	amlodipine 10 run-in valsartan/amlodipine 160/10 amlodipine 10	As for Study A2305
A2308	Safety/efficacy of valsartan/amlodipine compared to lisinopril/HCTZ in severe hypertensive patients (MSDBP ≥ 110 mmHg and <120 mmHg)	130	1-2 weeks 6 weeks	placebo run-in valsartan/amlodipine 160/5 titrated to valsartan/amlodipine 160/10 lisinopril/HCTZ 10/12.5 titrated to lisinopril/HCTZ 20/12.5	Safety was the primary endpoint. With respect to efficacy, the variables analyzed were identical to those in Study A2305.

- Dose response studies

Dose-findings studies were not conducted. The dose selection for the development program was based on the authorised doses of the respective monotherapies. The development program is in accordance with the CHMP guidance documents on evaluation of antihypertensives/fixed combinations.

- Main studies

Studies A2201 and A 2307

Study Participants, treatments, objectives
Studies A2201 and A2307 were double-blind, randomized, multifactorial, placebo-controlled, multicenter, parallel group trials, and had the same outcome measures. After the washout phase, patients went on to a 2-4 week single-blind placebo run-in period. If their MSDBP was within the prespecified range at the end of this period they were randomised to double-blind treatment for 8 weeks. Study A2201 used a factorial design with valsartan doses of 40, 80, 160, or 320 mg, amlodipine doses of 2.5 or 5 mg, and placebo. Study A2307 used a similar design with valsartan doses of 160 or 320 mg, amlodipine dose of 10 mg and placebo. A total of 1911 and 1250 patients were randomised in trial A2201 and A2307, respectively. The objective of these trials was to assess the blood pressure lowering effect of the various combinations compared to their monotherapy components and placebo. The primary efficacy variable was change from baseline in MSDBP at endpoint in all pivotal studies. Secondary variables were change in MSSBP, responder and control rates and standing MSDBP. All monotherapies and combinations were statistically different from placebo.

Results
Significant benefits of the combinations valsartan/amlodipine 80/5, 160/5 and 160/10 mg were demonstrated vs. monotherapy (amlodipine or valsartan) in studies A2201 and A2307. Several other

combinations showed benefit; however, these are not mentioned here, as they are not comprised of the present MAA. All changes from baseline in MSSBP were statistically different from placebo for all monotherapies and combinations. Furthermore, all combinations of valsartan/amlodipine for which MA is sought for, were statistically different from valsartan and amlodipine monotherapy. The observed mean reductions in MSDBP with the valsartan/amlodipine 80/5 mg and 160/5 mg doses are similar and the slope of the blood pressure dose response among the valsartan/amlodipine 5 mg dose groups is shallow in A2201. The blood pressure dose response among the valsartan monotherapy dose groups was more pronounced and one would have expected a similar pattern among doses of the combination as the dose of valsartan was increased. Therefore, this observed shallow dose response among the valsartan/amlodipine 5 mg dose groups may have been a play of chance due to usual variability in the study (individual 95% confidence intervals for the reduction in MSDBP are 13.99 [-15.31; -12.68], 14.23 [-15.54; -12.92] and 14.44 [-15.64; -13.24] mmHg for 160/5, 80/5 and 40/5 mg, respectively). From a clinical safety perspective, there was no dose related increase in adverse events (AEs) among the valsartan/amlodipine 5 mg treatment groups. In the double-blind, placebo-controlled studies, the incidence of adverse events in the valsartan/amlodipine 40/5, 80/5, 160/5, and 320/5 mg groups were 46.0%, 52.3%, 54.8%, and 46.5%, respectively, compared to 50.8% with amlodipine 5 mg.

Studies A2305 and A2306

Study Participants, treatments, objectives
The pivotal trials A2305 and A2306 adopted the same design. The design was in accordance with the requirements of the fixed combination section for second line therapy of the CHMP guidance on antihypertensives. After a wash-out phase, eligible patients were enrolled into a single-blind monotherapy phase with valsartan 160 mg and amlodipine 10 mg in study A2305 and study A2306, respectively, as to identify non-responders. These were subsequently randomised to continue monotherapy or shift to the fixed combinations of valsartan/amlodipine 160/5 mg or 160/10 mg in study A2305 or valsartan/amlodipine 160/10 mg in study A2306. Primary and secondary outcome measures were the same as in the placebo-controlled pivotal studies.

Results
In both studies a significant decrease of MSDBP as well as MSSBP at endpoint compared to baseline was evident for all treatment groups. In both studies MSDBP lowering was clinically and statistically superior with the combination therapies compared to the monotherapies. Furthermore, in study A 2305 valsartan/amlodipine 160/10 mg was statistically superior in comparison to valsartan/amlodipine 160/5 mg, although the clinical significance of this finding can be questioned.

Within treatment analyses for change from baseline MSDBP (from Applicant's tables 9-1, M5, 5.3.5.1. p6477 and 9039)

GROUP	BASELINE (MMHG)	**Mean change from baseline**	**95%CI for change**	**p-value**
Study A2305				
Val/Aml 160/10 mg	96.6	-11.4	-12.13, -10.64	< 0.0001
Val/Aml 160/5 mg	96.8	-9.6	-10.47, -8.82	< 0.0001
Val 160 mg	96.2	-6.6	-7.40, -5.74	< 0.0001
Study A2306				
Val/aml 160/10 mg	94.8	-11.8	-12.50, -11.06	< 0.0001
Aml 10 mg	95.3	-10.0	-10.73, -9.26	< 0.0001

The mean changes in MSDBP from baseline in the double-blind treatment period monotherapy arms of both studies (which were supposed to be the 'non-responders') showed a clinically relevant and statistically significant decrease over time during the double blind treatment period and reach -6.6 and -10.0 mmHg at endpoint for valsartan and amlodipine, respectively. It can thus be questioned whether the monotherapy period to identify the non-responders was sufficiently long and whether the true non-responders actually were identified. Even though the add-on studies were not optimal, the guideline's

claim of "a significant and clinically relevant additional blood pressure reduction of the combination" in comparison to either monotherapy could be proven.

Responder rates and proportions of patients with controlled hypertension (data from Applicant's tables 9-7 and 9-9, M5, 5.3.5.1. p6480 and 9043)

Group	Responder rate	Control rate
Study A2305		
Val/Aml 160/10 mg	81.0	75.3
Val/Aml 160/5 mg	68.0	62.4
Val 160 mg	56.8	52.6
Study A2306		
Val/aml 160/10 mg	79.0	77.8
Aml 10 mg	70.1	66.5

There was no dose-related increase in the incidence of adverse events in the valsartan/amlodipine 40/5, 80/5, 160/5, and 320/5 mg groups. Thus, from a benefit/risk perspective, there would appear to be no significant clinical concern in prescribing valsartan/amlodipine at either the 80/5 mg or 160/5 mg dose level and the choice can be left to the practicing physician on an individual patient basis. From a clinical practice perspective, a physician will initiate therapy in a hypertensive patient with valsartan 80 mg monotherapy and, depending on an individual patient's response and target blood pressure goal, may elect to increase the dose to valsartan 160 mg. A next logical step in the titration scheme for this patient would be the addition of amlodipine 5 mg. This step-wise approach is consistent with current hypertension treatment guidelines. In addition, the favourable benefit/risk profile of the valsartan/amlodipine 160/5 mg dose in this particular scenario was clearly demonstrated in study A2305.

Study A2308

Study Participants, treatments, objectives

Study A2308 was a study performed in patients with severe hypertension, patients' MSDBP had to be ≥110 and <120mmHg at randomization. The primary objective was to evaluate the safety of the fixed combination and only descriptive statistics are given for efficacy. After a short wash-out and placebo-run–in period approximately 60 patients per treatment group were randomized to either valsartan/amlodipine 160/5 mg or lisinopril/HCTZ 10/12.5 mg, i.e. the combination as first-line therapy which is not the scope of this application. Titration to valsartan/amlodipine 160/10 or lisinopril /HCTZ 20/12.5mg was foreseen if diastolic BP did not decrease sufficiently.

Results

From the provided data the treatment of the ACE inhibitor lisinopril in combination with the diuretic HCTZ appear "comparable" to the combination valsartan/amlodipine with respect to BP lowering, responder and control rates. Tolerability in this trial appeared to be unfavourable for the Valsartan/Amlodipine combination compared to the lisinopril/HCTZ combination. However, since Exforge is going to be used as a second line indication combined with the fact that the numbers of patient per treatment arm were small and comparisons therefore should be done with caution, this is acceptable.

Mean reductions in MSDBP and MSSBP (Applicant's table 4-7, M2, 2.5, p25)

MSDBP		MSSBP	
Valsartan/amlodipine N = 64	**Lisinopril/HCTZ N = 66**	**Valsartan/amlodipine N = 64**	**Lisinopril/HCTZ N = 66**
Mean change (SD)	Mean change (SD)	Mean change (SD)	Mean change (SD)
28.6 (7.7)	27.6 (8.6)	35.8 (11.8)	31.8 (14.7)

Responder and controlled patient rates (Applicant's table 4-8, M2, 2.5, p.26)

Responder rates		Control rates	
Valsartan/amlodipine N = 64 n (%)	Lisinopril/HCTZ N = 66 n (%)	Valsartan/amlodipine N = 64 n (%)	Lisinopril/HCTZ N = 66 n (%)
64 (100.0)	63 (95.5)	51 (79.7)	51 (77.3)

- Clinical studies in special populations

No studies in special populations have been performed. The analysis of efficacy and safety results indicates that there is a need for further data in the elderly. Therefore, the applicant was asked for a commitment to perform a separate study in elderly patients (see: follow-up measures). A paediatric development plan is not foreseen. Therefore no studies This is considered acceptable.

- Discussion on clinical efficacy

Documentation of efficacy is based on 5 pivotal studies. The primary efficacy variable was change from baseline in MSDBP at endpoint in all pivotal studies. Secondary variables were change in MSSBP, responder and control rates and standing MSDBP. Significant benefits of the combinations valsartan/amlodipine 80/5, 160/5 and 160/10 mg were demonstrated vs. monotherapy (amlodipine or valsartan) in studies A2201 and A2307. All changes from baseline in MSSBP were statistically different from placebo for all monotherapies and combinations. Furthermore, all combinations of valsartan/amlodipine for which MA is sought for, were statistically different from valsartan and amlodipine monotherapy. The observed mean reductions in MSDBP with the valsartan/amlodipine 80/5 mg and 160/5 mg doses are similar and the slope of the blood pressure dose response among the valsartan/amlodipine 5 mg dose groups is shallow in A2201. The blood pressure dose response among the valsartan monotherapy dose groups was more pronounced and one would have expected a similar pattern among doses of the combination as the dose of valsartan was increased. Therefore, this observed shallow dose response among the valsartan/amlodipine 5 mg dose groups may have been a play of chance due to usual variability in the study. The pivotal trials A2305 and A2306 adopted the same design. The eligible patients were enrolled into a single-blind monotherapy phase with valsartan and amlodipine to identify non-responders. These were subsequently randomised to continue monotherapy or shift to the fixed combinations of valsartan/amlodipine 160/5 mg or 160/10 mg in study A2305 or valsartan/amlodipine 160/10 mg in study A2306. In both studies a significant decrease of MSDBP as well as MSSBP at endpoint compared to baseline was evident for all treatment groups. In both studies MSDBP lowering was clinically and statistically superior with the combination therapies compared to the monotherapies. Furthermore, in study A2305 valsartan/amlodipine 160/10 mg was statistically superior in comparison to valsartan/amlodipine 160/5 mg, although the clinical significance of this finding can be questioned. The mean changes in MSDBP from baseline in the double-blind treatment period monotherapy arms of both studies (which were supposed to be the 'non-responders') showed a clinically relevant and statistically significant decrease over time during the double blind treatment period and reach -6.6 and -10.0mmHg at endpoint for valsartan and amlodipine, respectively. It can thus be questioned whether the monotherapy period to identify the non-responders was sufficiently long and whether the non-responders actually were identified. Even though the add-on studies were not optimal, the guideline's claim of "a significant and clinically relevant additional blood pressure reduction of the combination" in comparison to either monotherapy could be proven. From a clinical practice perspective, a physician will initiate therapy in a hypertensive patient with valsartan 80 mg monotherapy and, depending on an individual patient's response and target blood pressure goal, may elect to increase the dose to valsartan 160 mg. A next logical step in the titration scheme for this patient would be the addition of amlodipine 5 mg. This step-wise approach is consistent with current hypertension treatment guidelines. In addition, the favourable benefit/risk profile of the valsartan/amlodipine 160/5 mg dose in this particular scenario was clearly demonstrated in study A2305.

Clinical safety

Valsartan and Amlodipine are well known and characterized substances that are being used in combination. The rational for developing a fixed combination has been to produce either additive or synergistic reductions in blood pressure compared to the individual components with a lower incidence of side effects.

- Patient exposure

The number of patients treated with the intended dosages overall is in accordance with *ICH guideline E1A on the population exposure to assess clinical safety*. It should be noted that only 128 patients were exposure to the dosage of 80/5 for a median duration of only 28 days. The hypertension guideline states the following "There is a special need for data in elderly patients, including specific pharmacokinetic studies, dose-response curves and safety data and the number of subjects above 60 years should be proportional to the frequency of prescriptions." In order to get a rough estimate of the prescription frequency of Exforge one of its components were chosen. The use of CCA stratified to age in Denmark in year 2005 is shown below. These data were obtained from the Register of Medicinal Statistics at the Danish Medicines Agency, which is a database that contains figures on the total sale of medicinal products in Denmark.

Prescriptions of Calcium-antagonists (ATC code C08) in the year 2005 in Denmark

Age (years)	Number	%
0-64	400.831	38,3
65-74	277.764	26,6
> 75	366.880	35,1
Total	1.045.475	100,0

CHMP was aware of the fact that CCA have other indications than HTN, but the figures above reveal that more than 60% of the prescriptions have been issued to patients older than 65 years of age. Even though the figures are rough estimates for the expected use of Exforge, they strongly indicate the need for further efficacy and safety data in the elderly. Therefore, the applicant was asked for a commitment to perform a separate study in elderly patients (see: follow-up measures).

- Adverse events

A literature search for the combination therapy did not provide any unknown AE or AES. Adverse events by primary system organ class generally show comparable incidences between the valsartan/amlodipine group, the monotherapy groups and the placebo groups. The most frequently occurring AE in the total valsartan/amlodipine group was peripheral edema. It occurred at a significantly lower incidence than in the amlodipine monotherapy group ($p = 0.0009$). The incidence was higher compared to valsartan monotherapy ($p < 0.0001$) and placebo ($p = 0.0301$). For the other most common AEs of headache, nasopharyngitis, dizziness and upper respiratory tract infection, there was no significant difference between the incidence in the valsartan/amlodipine group and the valsartan monotherapy, amlodipine monotherapy, or placebo groups. In the table below the incidences of peripheral edema are shown.

Incidence of peripheral edema using fixed combination, monotherapy and placebo (Dataset A).

	Valsartan/amlodipine (mg)			**Amlodipine (mg)**			**Placebo**
	160/10	160/5	80/5	10	5	2.5	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total population	999	512	128	677	128	125	337
Edema peripheral	90 (9.0)	11 (2.1)	3 (2.3)	70 (10.8)	4 (3.1)	10 (8.0)	10 (3.0)

A clear dose-relationship is not apparent for peripheral edema when amlodipine is used as fixed combination or as monotherapy. The incidences were higher for the 2.5 and the 10 mg dose group than for the 5 mg dose group. Whether patients can be managed on a lower fixed combination dose

compared to monotherapy with respect to the incidence of adverse events is not supported by this application.

Summary data on safety are provided in tables below.

Adverse events by preferred term with incidence of 1% or more in the val/aml combination group (Applicant's table 5-5, M2, 2.5, p39)

	Valsartan/ amlodipine	Valsartan	Amlodipine	Lisinopril/ HCTZ	Placebo	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total population	2613	1229	930	66	337	5175
Patients with ≥ 1 AE	970 (37.1)	445 (36.2)	319 (34.3)	21 (31.8)	129 (38.3)	1884 (36.4)
Preferred term						
Edema peripheral	151 (5.8)	23 (1.9)	84 (9.0)	1 (1.5)	10 (3.0)	269 (5.2)
Headache	98 (3.8)	52 (4.2)	49 (5.3)	2 (3.0)	20 (5.9)	221 (4.3)
Nasopharyngitis	71 (2.7)	37 (3.0)	25 (2.7)	0 (0.0)	6 (1.8)	139 (2.7)
Dizziness	45 (1.7)	25 (2.0)	11 (1.2)	0 (0.0)	3 (0.9)	84 (1.6)
Upper RTI	43 (1.6)	13 (1.1)	12 (1.3)	0 (0.0)	7 (2.1)	75 (1.4)
Influenza	40 (1.5)	12 (1.0)	6 (0.6)	2 (3.0)	2 (0.6)	62 (1.2)
Diarrhea	36 (1.4)	16 (1.3)	4 (0.4)	4 (6.1)	5 (1.5)	65 (1.3)
Bronchitis	32 (1.2)	16 (1.3)	6 (0.6)	0 (0.0)	4 (1.2)	58 (1.1)
Cough	27 (1.0)	13 (1.1)	2 (0.2)	2 (3.0)	0 (0.0)	44 (0.9)
Back pain	25 (1.0)	25 (2.0)	13 (1.4)	1 (1.5)	2 (0.6)	66 (1.3)
Fatigue	25 (1.0)	11 (0.9)	10 (1.1)	0 (0.0)	5 (1.5)	51 (1.0)
Sinusitis	25 (1.0)	8 (0.7)	4 (0.4)	1 (1.5)	4 (1.2)	42 (0.8)

Suspected study drug related adverse events (Applicant's table 5-6, M2, 2.5, p40)

	Valsartan/ amlodipine	Valsartan	Amlodipine	Lisinopril/ HCTZ	Placebo	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total population	2613	1229	930	66	337	5175
Patients with ≥ 1 AE	306 (11.7)	86 (7.0)	132 (14.2)	7 (10.6)	27 (8.0)	558 (10.8)
Preferred term						
Edema peripheral	124 (4.7)	13 (1.1)	70 (7.5)	1 (1.5)	3 (0.9)	211 (4.1)
Headache	32 (1.2)	16 (1.3)	18 (1.9)	0 (0.0)	7 (2.1)	73 (1.4)
Dizziness	22 (0.8)	13 (1.1)	4 (0.4)	0 (0.0)	0 (0.0)	39 (0.8)
Diarrhea	12 (0.5)	3 (0.2)	2 (0.2)	0 (0.0)	2 (0.6)	19 (0.4)
Fatigue	12 (0.5)	6 (0.5)	5 (0.5)	0 (0.0)	0 (0.0)	23 (0.4)
Edema	11 (0.4)	1 (0.1)	5 (0.5)	0 (0.0)	0 (0.0)	17 (0.3)
Flushing	10 (0.4)	0 (0.0)	6 (0.6)	0 (0.0)	2 (0.6)	18 (0.3)
Joint swelling	10 (0.4)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	13 (0.3)
Somnolence	6 (0.2)	3 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	11 (0.2)
Vertigo	6 (0.2)	5 (0.4)	1 (0.1)	0 (0.0)	1 (0.3)	13 (0.3)
Asthenia	5 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	7 (0.1)
Cough	5 (0.2)	2 (0.2)	0 (0.0)	1 (1.5)	0 (0.0)	8 (0.2)
Dry mouth	5 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.1)
Nausea	5 (0.2)	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	9 (0.2)
Orthostatic hypotension	5 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)
Pitting edema	5 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.3)	7 (0.1)
Abdominal pain	4 (0.2)	2 (0.2)	1 (0.1)	0 (0.0)	1 (0.3)	8 (0.2)
Erythema	4 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.3)	7 (0.1)
Hot flush	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Tachycardia	4 (0.2)	2 (0.2)	3 (0.3)	0 (0.0)	0 (0.0)	9 (0.2)

- Serious adverse event/deaths/other significant events

Only one death occurred during the on-study treatment or follow-up periods of the 5 short-term studies (Dataset A) which. was not suspected to be related to study treatment. In addition one death occurred

during the on-study treatment or follow-up periods of the 2 long-term studies (Dataset C) which was also not suspected to be related to study treatment.
36 (0.7%) patients (32 on active treatment) in the double-blind, active- or placebo controlled population experienced an SAE. Incidences were similar for the different treatment groups and no pattern was evident for any of the treatment groups.

Summary data on SAEs and discontinuations due to SAEs are provided in table below.
Deaths, SAEs and discontinuations due to SAEs, dataset A (Applicant's table 5-8, M2, 2.5, p44)

	Valsartan/ amlodipine	Valsartan	Amlodipine	Lisinopril/ HCTZ	Placebo	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total population	2613	1229	930	66	337	5175
Deaths	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
SAEs	18 (0.7)	10 (0.8)	4 (0.4)	0 (0.0)	4 (1.2)	36 (0.7)
Discontinued due to AE(s)	63 (2.4)	10 (0.8)	30 (3.2)	0 (0.0)	7 (2.1)	110 (2.1)
SAE(s)	10 (0.4)	1 (0.1)	2 (0.2)	0 (0.0)	2 (0.6)	15 (0.3)

- Laboratory findings

There were no clinically meaningful changes in the haematology variables. For the clinical chemistry variables, the mean changes were generally not remarkable.

- Safety in special populations

An assessment of adverse events by age, gender, and race was conducted in dataset A. The overall AE incidence was slightly lower in Caucasian patients compared to those of other races. Peripheral edema occurred slightly more frequently in female patients and in those aged ≥ 65 years treated with valsartan/amlodipine or amlodipine monotherapy. No of these findings raises any concern. The analysis of efficacy and safety results indicates that there is a need for further data in the elderly. Therefore, the applicant was asked for a commitment to perform a separate study in elderly patients (see: follow-up measures). A paediatric development plan is not foreseen. This is considered acceptable.

- Discontinuation due to adverse events

The most common AEs which led to discontinuation in the valsartan /amlodipine and amlodipine monotherapy groups were primarily edema-related, in particular peripheral edema. This side effect is well known and well described. No other new side effect or shifts in frequencies were observed during these studies.

- Discussion on clinical safety

The primary safety database included 5175 patients who received at least one dose of study medication. Of these patients, 2613 received valsartan/amlodipine. In addition, 1649 patients from two long-term open-label studies were considered. The overall incidence of AEs was similar in valsartan/amlodipine, valsartan, amlodipine and placebo patients. The overall incidence of adverse events was not dose dependent. The most common AEs regardless of relationship to treatment in the valsartan/amlodipine group were peripheral oedema, headache, and nasopharyngitis. The incidence of peripheral oedema was somewhat lower in the valsartan/amlodipine patients when compared to amlodipine alone. The most frequent AEs suspected related to study drug the valsartan/amlodipine group were peripheral edema and headache. Changes in laboratory parameters observed with the combination of valsartan/amlodipine were modest. The overall incidence of serious AEs and AEs leading to study discontinuation in the valsartan/amlodipine group was low. No significant new adverse events were observed with long-term treatment. The main weakness of the safety database is the lack of studies in special populations and exclusion from the studies of the more fragile part of target patients. Overall is can be concluded that the fixed combination of amlodipine/valsartan in doses of 80/5, 160/5 and 160/10 mg does not cause any safety concerns.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system
The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. So far no serious risks for Exforge have been identified. Based on the results from the non-clinical and clinical development program, areas of potential risk and areas with limited information have been identified for continued pharmacovigilance.

The proposed pharmacovigilance plans by the MAA are considered suitable for identifying or characterising risks or providing missing information.

Risk Management Plan

The CHMP did not require the MAA to submit a risk management plan because FCP tablet consist of two well-known substances.

6. Overall conclusions, risk/benefit assessment and recommendation

The current clinical development program evaluated the efficacy and safety of Exforge in a population of patients with mild to moderate essential hypertension (Grade 1 and 2 in WHO classifications) whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

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. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology
Two well-described compounds are proposed in combination. In the SHR model, additive lowering effect on blood pressure was observed. The combination of amlodipine and valsartan is not expected to display concerns *in vitro* safety pharmacology studies (above reasons given by the applicant), wherefore non-clinical safety pharmacology studies the combination are not needed. The pharmacokinetics of each of the individual compounds has been sufficiently described; and, as based on the toxicokinetics studies of the combination, no significant impact on individual pharmacokinetics may be anticipated with FCP. The toxicological test species (rat, marmoset) were substantially exposed to both components of the product. Exposure of animals at NOAEL was mostly larger than that in humans at the highest dose (320:10), with human exposure multiples ranging from 0.3 to 32.5, indicating a moderate safety margin for humans.

Efficacy
The targeted indication for Exforge is treatment of hypertension where monotherapy is not sufficient. Documentation of efficacy is based on 5 pivotal studies. The study program demonstrated that the blood pressure lowering effect of Exforge 80/5, 160/5 and 160/10 mg compared to their monotherapy components and placebo were statistically significantly different from placebo and the monotherapies. Both add-on studies (A2305 and A2306) showed a lowering of MSDBP that were clinically and statistically superior with the combination therapy compared to the monotherapies. However, the study design may have failed to identify the "non-responders" adequately but the guideline's claim of "a significant and clinically relevant additional blood pressure reduction of the combination" in comparison to either monotherapy is fulfilled. In study A2308 in patients with severe hypertension Exforge is used in a first line indication and not in a second line indication, which the MAA was applying for. In the opinion of CHMP the data from this study can be however extrapolated to the targeted population. The development program of Exforge included a low number of elderly patients; out of 2600 patients exposed to valsartan/amlodipine 542 patients were ≥ 65 years and only 114 patients (4%) ≥ 75 years. As this is unlikely to correspond to the real life situation the CHMP

proposed a commitment to confirm the efficacy and safety in an elderly population. Valsartan and Amlodipine are well known and characterized substances that are being used concomitantly. A literature search for the concomitant therapy did not provide any unknown AE or AES.

Safety
From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. Valsartan and Amlodipine are well known and characterized substances that are being used in combination. A literature search for the combination therapy did not provide any unknown AE or AES. The study program does not disclose any safety concerns.

- User consultation

The company commit to conduct a new user testing of its PL as one of the follow-up measures.

Risk-benefit assessment

The clinical development program for valsartan/amlodipine fixed combination products included the bioequivalence studies and phase III clinical efficacy/safety studies. In line with the guidance documents (*Note for Guidance on Fixed Combination Medicinal Products, CPMP/EWP/240/95; Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, CPMP/EWP/238/95 Rev. 2*) it consisted of placebo and active controlled studies performed in order to justify the second line use of the fixed combination and the proposed dosages. Bioequivalence data have been provided to bridge from the trial formulations to the intended commercial formulation. The application for Exforge in the opinion of CHMP has a favourable risk/benefit ratio providing the applicant commits to perform a number of post authorisation follow-up measures to be reported back to the CHMP within predefined timeframes. A justification for not providing the risk management plan was submitted by the Applicant. The CHMP did not require the MAA to submit it because FCP consist of two well-known substances. The CHMP, having considered the data submitted, was of the opinion that the 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 in the treatment of essential hypertension was favourable and therefore recommended the granting of the marketing authorisation.