Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Australian Public Assessment Report

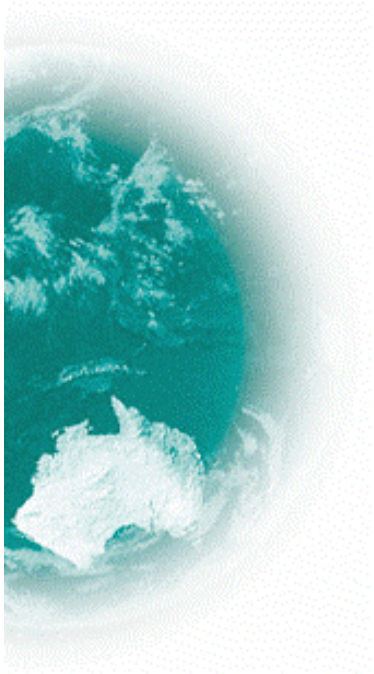
for

Amlodipine (as besylate) and Valsartan and Hydrochlorothiazide

Proprietary Product Name: Exforge HCT, Ejocia HCT

Submission No: PM-2008-03499-3-3

Sponsor: Novartis Pharmaceuticals Australia Pty Limited



August 2010

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	New fixed combination
Decision:	Approved
Date of Decision:	1 April 2010
Active ingredient(s):	Amlodipine (as besylate) Valsartan Hydrochlorothiazide (HCT)
Product Name(s):	Exforge HCT, Ejocia HCT
Sponsor's Name and Address:	Novartis Pharmaceuticals Australia Pty Limited 54 Waterloo Road North Ryde NSW 2113
Dose form(s):	Film-coated tablet
Strength(s):	5 mg/160 mg/12.5 mg of amlodipine/valsartan/HCT 5 mg/160 mg/25 mg of amlodipine/valsartan/HCT 10 mg/160 mg/12.5 mg of amlodipine/valsartan/HCT 10 mg /160 mg/ 25 mg amlodipine/valsartan/HCT 10 mg /320 mg/25 mg of amlodipine/valsartan/HCT
Container(s):	PA/Al/PVC//Al Blisters
Pack size(s):	7, 14, 28, 30 and 56 tablets
Approved Therapeutic use:	ONLY as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of amlodipine, valsartan and hydrochlorothiazide taken either as three single component formulations or as dual-component formulation with a single component formulation, all components at the same dose level. Treatment should not be initiated with these fixed-dose combinations (see "Dosage and Administration").
Route(s) of administration:	Oral
Dosage:	Same dose as used with individual components
ARTG Numbers:	157954, 158161, 158162, 158163, 158164, 158165, 158166, 158167, 158168, 158169

Product Background

This submission is to register the abovementioned new fixed-dose combination tablets which contain 5 or 10 mg of amlodipine (as amlodipine besylate), 160 mg or 320 mg of valsartan and 12.5 mg or 25 mg of hydrochlorothiazide (HCT). Two trade names are proposed: Exforge HCT and Ejocia HCT. The product will be referred to as Exforge HCT for the remainder of this document.

It is proposed that these tablets will be indicated as a substitution therapy in patients (that is, patients are not to be started on this combination therapy). The indications being: "*for the treatment of hypertension. As a replacement therapy in patients whose blood pressure is adequately controlled on amlodipine, valsartan and HCT used as individual or combination therapies*".

Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Valsartan as monotherapy (Diovan and other trade names) is sponsored by Novartis and is marketed in four dosage strengths 40 mg, 80 mg, 160 mg and 320 mg. Its registered indications are as follows:

Treatment of hypertension

Treatment of heart failure (NYHA class II-IV) in patients receiving usual therapy (for example diuretics, digitalis) who are intolerant of ACE inhibitors

To improve survival following myocardial infarction in clinically stable patients with clinical or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction

Novartis Pharmaceuticals Australia Pty Ltd (Novartis) is the innovator of the drug substance valsartan. They have registered the following products containing valsartan. These products are all indicated for the treatment of hypertension, but the combinations products have the qualifying statement that 'treatment should not be initiated with these combinations'. There are no generic products containing valsartan.

Brand Name (active ingredient(s))	*Dose Form and Strength*	*AUST R*
Diovan Capsules (valsartan)	80 mg	63970, 63972
	160 mg	63971, 63973
Diovan Tablets[1] (valsartan)	40 mg	93165
	80 mg	80868
	160 mg	80871
	320 mg	123357
Co-Diovan Tablets[2] (valsartan/HCT)	80 mg/ 12.5 mg	96740
	160 mg/12.5 mg	96741
	160 mg/25 mg	96742
	320 mg/ 12.5 mg	135782
	320 mg/25 mg	135812
Exforge Tablets[3] (amlodipine besylate/valsartan)	5 mg/80 mg	130787
	5 mg/160 mg	130834
	10 mg/160 mg	130841

Amlodipine is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. It is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Amlodipine as a monotherapy is not sponsored by Novartis but by Pfizer (Norvasc) as the innovator and a number of generic companies. It is available in 3 dosage strengths: 2.5 mg, 5 mg and 10 mg and its registered indications are as follows:

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[1] Novartis have added the following brand names: Tareg (AUST R 151559, 151560, 151563, 151566) and Oflytro (AUST R 155736, 15737, 155740, 155743).

[2] Novartis have added the following brand names: Co-Tareg (AUST R 1152764, 152765, 152766, 152767, 152767) and Oltalia (AUST R 1152449, 152470, 152761, 152762, 152763).

[3] Novartis have added the following brand name: Ejocia (AUST R 151626, 151627, 151628).

Hypertension: TRADENAME is indicated for the first line treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single antihypertensive agent may benefit from the addition of TRADENAME, which has been used in combination with a thiazide diuretic, beta adrenoceptor blocking agent or an angiotensin-converting enzyme inhibitor.

Angina: *TRADENAME is indicated for the first line treatment of chronic stable angina. TRADENAME may be used alone, as monotherapy or in combination with other antianginal drugs*.

HCT inhibits the active reabsorption of sodium, mainly in the distal kidney tubules and promotes the excretion of sodium, chloride and water. The renal excretion of potassium and magnesium increases dose-dependently, while calcium is reabsorbed to a greater extent. HCT decreases plasma volume and extracellular fluid and reduces cardiac output and blood pressure. During long-term therapy, reduced peripheral resistance contributes to the blood pressure reduction.

Monotherapy tablets containing the diuretic HCT have been registered for many years for the use in the treatment of hypertension and there are a number of other fixed dose combination tablets using this drug substance. Novartis does not have an HCT monotherapy product, but as mentioned above it does have a fixed-dose combination product containing valsartan and HCT.

There is currently one strength of Dithiazide (HCT monotherapy), 25 mg ,on the Australian Register of Therapeutic Goods (ARTG) which is approved for:

Hypertension: May be used alone or in combination with other antihypertensive drugs.

Oedema: Associated with congestive heart failure, hepatic cirrhosis, nephrotic syndrome, acute glomerulonephritis, chronic renal failure, premenstrual tension and drug induced oedema".

For hypertension, the usual starting dose is 25 or 50 mg a day as a single or divided dose and the dosage should be adjusted according to blood pressure response. The maximum recommended daily dose is 100 mg. In the approved product information (PI) there is a further note that when thiazides are used with other antihypertensives, the dose of the latter may need to be reduced to avoid excessive decrease in blood pressure.

As noted in the table above, the combination of valsartan and HCT (Co-Diovan, Co-Tareg, Oltalia) is registered and sponsored in Australia by Novartis. It is available in five dosage strengths: 80/12.5, 160/12.5, 160/25, 320/12.5 and 320/25 mg. It is approved for the following indications:

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

The combination of amlodipine and valsartan (Exforge, Ejocia) is also registered and sponsored in Australia by Novartis. It is available in 3 dosage strengths: 5/80, 5/160 and 10/160 mg and there are submissions currently under evaluation for the 2 dosage strengths: 5/320 & 10/320 mg. It is approved for the following indications:

TRADENAME is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed dose combination.

Regulatory Status

Similar applications to the current Australian submission have been submitted in the European Union (EU), USA and Switzerland. It was approved in the EU on 21 October 2009 for the following indication:

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

The application was approved by the US FDA on 30 April 2009 for the indication:

Treatment of hypertension. Not indicated for initial therapy.

The application was approved in Switzerland on 16 September 2009 for the indication:

Treatment of essential hypertension. Exforge HCT is indicated in patients whose blood pressure is not adequately controlled by dual therapy.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substances (active ingredients)

Details relating to all drug substances have been evaluated before. Structures are detailed below. All details relating to valsartan are the same as for the registered products. The specifications are the same as those in the USP32 monograph for valsartan with an additional test and limits for particle size distribution and residual solvents.

There are EP/BP2009 and USP32 monographs for HCT and BP2009 and USP32 monographs for HCT tablets.[4]

There is an EP/BP2009 monograph for amlodipine besilate[5] and a USP32 monograph for amlodipine besylate, but no monographs for finished products containing this drug substance.

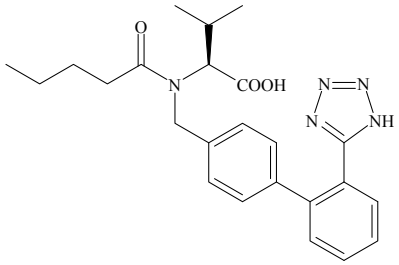
There is no BP monograph for valsartan or any dosage forms containing this drug substance, but there is a USP32 monographs for valsartan drug substance and valsartan and HCT tablets.

Three different manufacturers are used for the amlodipine besylate used in the products. The material from each is covered by an EDQM Certificate of Suitability (CEP) certifying that the material meets the EP/BP2009 monograph for amlodipine besilate. In addition, the finished product manufacturer has adopted additional tests and limits for particle size distribution, residual solvents and alkyl besylates (which are genotoxic and can be formed from besylate ions and ethanol, methanol or iso-propanol used in the manufacture). The Medicines Toxicology Evaluation Section of the TGA (MTES) stated that the limit of 75 ppm of each of these alkyl besylates was acceptable.

Two different manufacturers are used for the HCT used in these products. A CEP was provided for one site certifying that the material meets the EP/BP2009 monograph for HCT and an acceptable Drug Master File was provided for the other site. In addition, the finished product manufacturer has adopted additional tests and limits for particle size distribution and residual solvents.

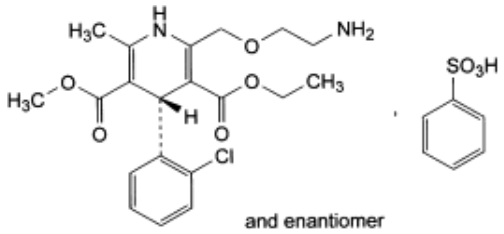
[4] USP: United States Pharmacopoea, EP: European Pharmacopoea, BP: British Pharmacopoea

[5] Note the Australian Approved Name (AAN) at the time of writing is amlodipine besylate and not amlodipine besilate.



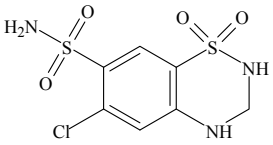
valsartan

***Chemical Name*:**
N-pentanoyl-N-[2'-(1H-tetrazole-5-yl)biphenyl-4-ylmethyl]-L-valine
CAS Number: [137862-53-4]
Molecular Formula: $C_{24}H_{29}N_5O_3$
Molecular Weight: 435.5
Description: A white to practically white microcrystalline powder
Solubility in Water: Slightly soluble (1.0-10 mg/mL, 0.1-1.0%)



amlodipine besylate

Chemical Name:
3-ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate
CAS Number: [111470-99-6] ([88150-42-9] for free base)
Molecular Formula: $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$
Molecular Weight: 567.1 (408.9 for free base)
Description: A white to almost white powder
Solubility in water: Slightly soluble (1.0-10 mg/mL, 0.1-1.0%)



HCT

Chemical Name:
6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide
CAS Number: [58-93-5]
Molecular Formula: $C_7H_8ClN_3O_4S_2$
Molecular Weight: 297.7
Description: A white to almost white powder
Solubility in water: Very slightly soluble (~0.6 mg/mL, 0.06 %w/v) over pH range 1.0-7.4

Drug Product

Formulation and manufacture

The tablets are to be manufactured by Novartis Pharma Stein AG in Switzerland. This is achieved by simple dry compression involving mixing, screening, roller compaction, final blending, compression, film-coating, drying and packaging. The tablets contain no unusual excipients and the quality of the excipients is adequately controlled. No material of animal origin is used.

The cores of the 5/160/12.5 and 10/320/250 tablets are direct scales, and other strengths are based on the 5/160/12.5 tablet with the different amounts of the drug substances being compensated for with different amounts of microcrystalline cellulose. Although the tablets are all the same shape, the four lower strength tablets are distinguished by colour and markings. The highest strength is the same colour as the 10/160/25 tablet, but is significantly larger and also has different markings. Finally, the strengths are further distinguished by different colour packagings.

Specifications

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

The dissolution limits are appropriate. The highest strength uses a paddle speed of 55 rpm compared to 50 rpm for other tablets. This is due to the larger tablet causing coning.

After the limit for total degradants was tightened, the specifications were considered acceptable.

Stability

Stability data was provided to support the proposed shelf lives of 2 years when stored below 30ºC in opaque PA/Al/PVC // Al blister packs. The storage conditions 'protect from moisture' and 'protect from light' also apply.

Biopharmaceutics

Clinical Background

The pivotal Phase III efficacy studies (VAA A2201E1, VEA A2302 and VEA BR01) were performed with co-administration of single entity amlodipine capsules, valsartan capsules and HCT capsules (A2201E10), or single entity amlodipine capsules, valsartan capsules and HCT capsules (A2302) or with co-administration of valsartan/ HCT combination tablets and amlodipine tablets (BR01).

- The 2.5 and 5 mg amlodipine capsules used in studies A2201E1 and A2302 were over-capsulated Norvasc tablets purchased in the US.
- The 5 and 10 mg amlodipine tablets used in study BR01 were Norvasc tablets purchased in the US.
    - An over-capsulated 5 mg tablet and an over-capsulated 10 mg tablet were used in bioequivalence studies 2305 and 2306, respectively. It is accepted that all these products will be bioequivalent to each other at the same dose as study 2105 demonstrated equivalence of the 5 mg tablet with the 5 mg overcapsulated tablet and amlodipine is BCS Class 1.[6]

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

- The contents of the 80 and 160 mg valsartan capsules used in study A2201E1 were identical to the contents of the Diovan capsules registered in Australia.
- The 160 mg valsartan tablets used in study A2302 were identical to the Diovan tablets registered in Australia.
- The 12.5 and 25 mg HCT capsules used in studies A2201E1 and A2302 were the same formulation capsules used in bioequivalence studies 2305 and 2306.
- The 160/12.5 mg valsartan and HCT combination tablet used in study BR01 were identical to the Co-Diovan tablet registered in Australia.

Studies submitted

Four bioavailability studies and a food effect study have been submitted. Each study used an appropriate study design and appropriately validated test methods for the determination of amlodipine, valsartan and HCT were used.

Study VEA489A 2305

This was a 4-way cross-over study in 32 subjects comparing the relative bioavailability of the proposed *5/160/12.5* tablet (and two other triple combination tablets) to the bioavailability from a dose consisting of the registered 160 mg valsartan Diovan tablet, an overseas 5 mg amlodipine capsule (over-capsulated US Norvasc 5 mg tablet[7]) and an overseas 12.5 mg HCT capsule[8].

Only 26 subjects completed the study and one subject was removed from the sponsor's calculations in relation to valsartan and one subject was removed from the sponsor's calculations in relation to amlodipine as these subjects returned unusually low results when receiving the individual monotherapies. The sponsor's statistical results otherwise used all available datasets and submitted the results below (Table 1).

Table 1: Study No. VEA489A2305 – PK Data for Combinations

Table 11-5 Summary of Statistical Analysis of Relative Bioavailability of VEA489A fixed combinations compared to CSF free combination

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

CSF free combination is the reference treatment.

Subjects 5122 and 5112 excluded from Valsartan and Amlodipine analyses, respectively.

[7] As used in clinical study A2302

[8] As used in clinical studies A2201E1 and A2302

These results suggest that the *5/160/12.5* tablet proposed for supply in Australia (Prototype 1) is bioequivalent with respect to both the maximal plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC) to the individual monotherapies used in the clinical studies in relation to all of the analytes.

However, in response to questioning the sponsor had no valid reason for not using the valsartan data from the outlier subject in the statistical calculations. If the results for this subject are included the 90% confidence intervals (CIs) for valsartan become 0.93-***1.29*** for C_{max} and 0.95-***1.39*** for AUC_{0-t}: that is; bioequivalence can no longer be concluded. The inclusion of the outlier subject in the amlodipine analysis did not affect the validity of the results.

The evaluator repeated the statistical calculations relating to valsartan using only datasets from the 26 subjects that completed the study and not all available datasets. The 90% CIs then became 0.84-***1.255*** for C_{max} and 0.88-1.21 for AUC_{0-t} with the outlier subject and ***0.79***-1.11 for C_{max} and 0.84-1.11 for AUC_{0-t} without the outlier subject. In either case bioequivalence is observed for AUC, but not for C_{max}.

Given that the unusual result was observed for the monotherapy and not the proposed fixed-dose combination tablet, the evaluator was of the opinion that the weight of evidence is in favour of concluding bioequivalence of the valsartan response for the proposed tablet versus the monotherapies used in the clinical studies. This evidence also includes the results from study VEA489A 2306 (see below) and the similarity of the tablet formulations of the different strengths. Nonetheless, the results of this study were brought to the attention of the Delegate.

Study VEA489A 2306

This was a 3-way cross-over study in 30 subjects (28 completing) comparing the relative bioavailability of the proposed *10/160/25* tablet (and one other triple combination tablet) to the bioavailability from a dose consisting of the registered 160 mg valsartan Diovan tablet, an overseas 10 mg amlodipine capsule (over-capsulated US Norvasc 10 mg tablet[9]) and an overseas 25 mg HCT capsule[7].

The sponsor's statistical results (Table 2) were accepted by the evaluator.

[9] The un-capsulated tablet was used in clinical study BR01.

Table 2: Statistical Analysis arising from Study VEA489A 2306

Table 11-5 Summary of statistical analysis of relative bioavailability of valsartan, HCTZ and amlodipine following a single oral dose of 160/25/10 mg valsartan/HCTZ/amlodipine fixed combination tablet (prototype I and II) compared with free combination CSFs of 160 mg valsartan, 25 mg HCTZ and 10 mg amlodipine

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

CI = confidence interval; PK = pharmacokinetic; HCTZ = hydrochlorothiazide; CSF = clinical service form

These results indicate that the *10/160/25* tablet proposed for supply in Australia (Prototype 1) is bioequivalent with respect to both C_{max} and AUC to the individual monotherapies used in the clinical studies in relation to all of the analytes.

Study VEA489A 2105

This was a 2-way cross-over study in 24 subjects (all completed) comparing the relative bioavailability of the 5 mg amlodipine capsule used in clinical study A2302 and bioavailability study A2305 with the non-capsulated 5 mg US Norvasc tablet (used in clinical study BR01).

The results of this study were accepted without recalculation by the evaluator because the study design and sampling times were appropriate, neither of the two formulations are known to be registered in Australia and the sponsor's calculations in studies 2305 and 2306 have been confirmed as being correct.

The results indicate that these two overseas formulations are bioequivalent with respect to C_{max} (90% CI = 0.93-1.04) and AUC_{0-t} (90% CI = 0.94-1.02).

Study VEA489A 2106

This was a 2-way cross-over study in 26 subjects (23 completed) and compared the relative bioavailability of amlodipine from the proposed *10/160/25* tablet to that from a dose consisting of the registered 160 mg valsartan Diovan tablet, an overseas 10 mg amlodipine tablet (EU Istin 10 mg tablet[10]) and an overseas 25 mg HCT capsule[7].

The results of this study were accepted without recalculation by the evaluator because the study design and sampling times were appropriate, the study only determined amlodipine levels and the amlodipine tablet was not purchased in Australia, and the sponsor's calculations in studies 2305 and 2306 have been confirmed as being correct.

The results indicate that for amlodipine the proposed *10/160/25* tablet is bioequivalent with respect to C_{max} (90% CI = 0.92-1.02) and AUC_{0-t} (90% CI = 0.91-1.01) to the overseas monotherapy amlodipine tablet.

[10] As used in clinical study A2302

Study VEA489A 2310

This was a 2-way cross-over study in 36 subjects (33 completed) to determined the effect of food (high fat breakfast) on the proposed *10/320/25* tablet.

The results of this study were also accepted without recalculation by the evaluator.

The results indicate:

- A 10% increase in amlodipine levels with food, but not sufficient to take the 90% CIs outside 0.80-1.25 (C_{max} = 1.05-1.18 and AUC_{0-t} = 1.03-1.15).
- A 14% increase in valsartan levels with food which was sufficient to take the 90% CIs outside of 0.80-1.25 (C_{max} = 0.98-***1.29*** and AUC_{0-t} = 0.99-***1.31***).
- A 10% increase in HCT AUC, but not sufficient to take the 90% CIs outside 0.80-1.25 (AUC_{0-t} = 1.02-1.18) and a 10% decrease in HCT C_{max} which was sufficient to take the 90% CIs outside of 0.80-1.25 (C_{max} = ***0.79***-0.93).

These results were brought to the attention of the Delegate as they are at odds with the food statements in the product information (PI).

Justifications submitted for non-supply of bioavailability/bioequivalence data

No bioavailability data has been provided comparing the proposed *5/160/25*, *10/160/12.5* and *10/320/25* tablets to either any of the other proposed triple combination tablets (*5/160/12.5* and *10/160/25*) or to a dose consisting of single amlodipine, valsartan and HCT tablets. A justification for this omission was provided. The chemistry and quality control aspects, and the clinical aspects, were acceptable.

The sponsor referred to previously provided justifications for using the overseas amlodipine and HCT products in the bioavailability and clinical studies rather than products available in Australia. Those justifications were relevant to this submission and acceptable.

Other bioavailability comments

The submission did not include a cross-over study to determine whether there are any pharmacokinetic interactions between amlodipine, valsartan and HCT. Instead, details were provided of a multi-centre, parallel study (VEA489A 2104). As this is a pharmacokinetic study and not a bioavailability study, it has not been evaluated by the quality evaluator. For completeness, this study concluded that:

<u>valsartan</u>

- increased the AUC of HCT by 8% (90% CI = 0.89-1.32)
- decreased the C_{max} of HCT by 17% (0.69-0.99)
- increase the AUC of amlodipine by 9% (0.90-1.32)
- increased the C_{max} of amlodipine by 9% (0.90-1.32);

<u>HCT</u>

- increased the AUC valsartan by 25% (0.98-1.59)
- increased the C_{max} of valsartan by 22% (0.98-1.52)
- increase the AUC of amlodipine by 10% (0.91-1.33)
- increased the C_{max} of amlodipine by 9% (0.92-1.32);

<u>amlodipine</u>

- increased AUC valsartan by 10% (0.88-1.37)

- increased the C_{max} of valsartan by 15% (0.94-1.41)
- did not affect the bioavailability of HCT (AUC = 0.86-1.24 and C_{max} = 0.86-1.20).

However, these results somewhat differ from previous cross-over studies evaluated in relation to the registered fixed-dose double combination products. Thus:

valsartan

- decreased the AUC of HCT by 31% (0.55-0.85)
- decreased the C_{max} of HCT by 26% (0.61-0.91)

HCT

- decreased the AUC valsartan by 13% (0.72-1.04)
- decreased the C_{max} of valsartan by 19% (0.63-1.05)

valsartan

- did not affect the AUC of amlodipine (0.81-1.07)
- decreased the C_{max} of amlodipine by 15% (0.69-1.04)

amlodipine

- not affect the bioavailability of (AUC = 0.96-1.08 and C_{max} = 0.98-1.16)

These results were brought to the attention of the Delegate.

No data on the absolute bioavailability of the tablets has been provided. However, given the results of the studies provided, it will be accepted that results for the proposed fixed-dose combination tablets are similar to those for the relevant monotherapy tablets.

Quality Summary and Conclusions

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

With respect to bioavailability, data was provided:

- That is purported to demonstrated bioequivalence of amlodipine, valsartan and HCT when administered as the combination amlodipine, valsartan and HCT tablets to amlodipine, valsartan and HCT when administered as a co-administration of monotherapy tablets. This was the case for one of the studies provided, but in for the other study it was not unequivocal in relation to valsartan.
- That shows that food causes a slight increase in the bioavailability of valsartan, but has no effect on amlodipine and only a very slight affect on the C_{max} of HCT when the three drugs are administered as the combination tablets.
- That there are variable (though mostly not large) pharmacokinetic interactions between drug substances.

The Delegate will need to decide if these observations are clinically important.

III. Nonclinical Findings

Introduction

The data presented were of an acceptable quality. The studies examining pharmacokinetics and repeat-dose toxicity were performed according to Good Laboratory Practice (GLP) standards.

The sponsor proposes to market Exforge HCT tablets, which combine three drugs that act via independent mechanisms to reduce blood pressure. The combination is intended for use by persons

above the age of 18 years who require additional blood pressure control beyond that provided by drug monotherapy or by dual combination therapies. The three drugs combined in Exforge HCT tablets are: amlodipine, a dihydropyridine-class, calcium channel blocker that lowers blood pressure by relaxing smooth muscle in vessel walls; valsartan, an inhibitor of the angiotensin AT_1 receptor (activation of which has various blood pressure-raising effects); and HCT, a thiazide class diuretic that acts on kidneys to reduce water reabsorption. The choice of drugs used in the combination is based on their pharmacological properties, lack of pharmacokinetic interaction, and their clinical effectiveness.

Pharmacology

The mechanism of action of all three drugs in the combination is well established and each individual drug has a history of extensive research, regulatory review and postmarket experience. Accordingly, it is acceptable that no pharmacology (primary, secondary or safety) studies were submitted by the sponsor.

Pharmacodynamic interactions

No specific studies were submitted investigating the potential pharmacodynamic interaction between valsartan, HCT and amlodipine or between the drug combination and other drugs.

Pharmacokinetics

The pivotal pharmacokinetics (PK) were obtained as part of an examination of the toxicology of the triple combination: groups of rats were given a once-daily oral (gavage) dose of amlodipine/valsartan/HCT (2:32:5) at 0.5:8:1.25, 2:32:5, or 4:64:10 mg/kg for 13 weeks. Three other groups of rats were dosed with the individual components at the same dose as was present in the highest dose (HD) combination study (that is, amlodipine at 4 mg/kg/day, valsartan at 64 mg/kg/day, or HCT at 10 mg/kg/day). The major conclusions from the study were:

(1) For all three compounds, whether administered alone or in combination, uptake following oral administration was quite rapid with time to maximal plasma concentration (T_{max}) values of around 0.5-2 hours after dosing.

(2) Exposure to amlodipine, valsartan, and HCT, whether administered alone or in combination, increased approximately linearly with dose in both male and female rats.

(3) Amlodipine exposure on Day 1 of dosing was about 50% higher in female than in male rats, however, there was little difference by Week 11 of dosing. Valsartan and HCT showed no significant gender effects.

(4) In both sexes and all dose groups, amlodipine exposure during Week 11 was higher than that on Day 1. In contrast, valsartan exposure values during Week 11 were consistently lower than those seen on Day 1. HCT exposure was comparable in both sexes and at both measurement times.

(5) Co-administration appeared to have little or no effect on exposure values for amlodipine, valsartan, and HCT, suggesting a lack of significant drug interaction.

Published studies have shown that both amlodipine and valsartan bind to serum albumin and to α_1-acid glycoprotein, whilst HCT binds to undefined serum proteins.

The sponsor did not perform tissue distribution or metabolism and excretion studies. Published results indicate that amlodipine is converted to various metabolites and (in humans) predominantly excreted in urine; valsartan is largely excreted unchanged via faeces; and HCT is largely excreted unchanged in urine.

PK Drug Interactions

There was no PK interaction between valsartan, HCT and amlodipine (see above). Nonclinical PK interaction studies between the triple combination (or its components) and other drugs were not

performed by the sponsor. Published results indicate that amlodipine, which is metabolised by and also inhibits CYP3A4, can interact with other drugs that are metabolised by CYP3A4. Both valsartan and HCT are known to undergo limited metabolism and show little inhibitory activity towards CYP enzymes, and hence are unlikely to interfere with CYP-mediated metabolism of other drugs.

Toxicology

Relative exposure

Exposure ratios were derived by dividing rat area under the plasma concentration time curve from time zero to 24 hours ($AUC_{0\text{-}24\ h}$) values by $AUC_{0\text{-}24\ h}$ values from male and female hypertensive humans given the maximum recommended amlodipine/valsartan/HCT dose (Table 3). The maximum recommended daily dose of Exforge HCT for humans is one 10:320:25 mg tablet (corresponding to 10 mg of amlodipine, 320 mg of valsartan, and 25 mg of HCT). While separate exposure ratio values are given for male and female rats at each dose the values were generally similar for both sexes.

It is notable from Table 3 that exposure ratio values for amlodipine and valsartan in the pivotal 13-week toxicology study only reach a maximum of around 1 (that is, comparable with human exposure at maximum dose), at doses well in excess of the No Observable Adverse Effect Level (NOAEL). HCT exposure ratios were higher than those of the two other drugs in the 13-week experiment, but were still only around 0.5 at the NOAEL.

Table 3: Relative exposure to amlodipine, valsartan, and HCT during rat repeat-dose toxicology studies (The NOAELs[b] are bolded and underlined)

Study no.	Dosing duration (Sample time)[a]	Drug dose (mg/kg/ d)[c]	Drug	Sex	$AUC_{0\text{-}24\ h}$ (ng.h/ mL)	Exposure ratio[e]
0670714	14 days (day 13-14)	**4:64:10**	Amlod.[d]	M	708	1.40
				F	542	1.07
			Valsart.[d]	M	80,300	0.97
				F	36,800	0.45
			HCT[d]	M	20,570	10.45
				F	4,400	2.23
		8:128:20	Amlod.	M	565	1.12
				F	2,072	4.11
			Valsart.	M	15,400	0.19
				F	140,000	1.69
			HCT	M	16,800	8.53
				F	22,090	11.22
0670715	13 weeks (week 11)	**0.5:8:1.25**	Amlod.	M	40.9	0.08
				F	65.6	0.13
			Valsart.	M	6,370	0.08
				F	4,940	0.06
			HCT	M	888	0.45

		F	939	0.48
2:32:5	Amlod.	M	368	0.73
		F	460	0.91
	Valsart	M	14,500	0.18
		F	24,500	0.30
	HCT	M	3090	1.57
		F	3590	1.82
4:64:10	Amlod.	M	802	1.59
		F	817	1.62
	Valsart	M	70,200	0.85
		F	35,100	0.42
	HCT	M	10,300	5.23
		F	6,870	3.49
Individual drugs[f]	Amlod.	M	931	1.84
		F	1,100	2.18
	Valsart	M	45,700	0.55
		F	38,700	0.47
	HCT	M	6,100	3.10
		F	5,640	2.86

[a]Consecutive days of drug dosing (figure in brackets is day on which analysis of drug pharmacokinetics was performed); [b]No observed adverse effect level for combination dosing with amlodipine/valsartan/HCT.
[c]Amlodipine/valsartan/HCT.; [d]Amlod. = amlodipine; valsart. = valsartan; and HCT = HCT; [e]AUC value at given dose divided by AUC value at maximum recommended human dose (see text for further details); [f]Amlodipine at 4 mg/kg/day, valsartan at 64 mg/kg/day, or HCT at 10 mg/kg/day.

Repeat-dose toxicity

All repeat-dose studies used the orally administered amlodipine/valsartan/HCT combination and were conducted in rats. Animals were dosed once per day by gavage. The studies were performed by established pharmacology laboratories according to GLP procedures, and used both sexes and standard testing times and group numbers.

No novel toxicities were observed in the submitted amlodipine/valsartan/HCT repeat dose studies. The reversible toxicological findings noted have previously been observed as exaggerated pharmacological effects of one or more of the individual components.

Increases in serum creatinine and urea, renal juxtaglomerular hyperplasia, erosions in the glandular stomach, decreased heart weight, decreased erythroid parameters and decreased reticulocytes have previously been noted with valsartan administration. The prolonged hypotensive effect of valsartan leads to decreased renal perfusion and subsequent ischemia, which results in decreased serum urea and creatinine. This is a class effect of drugs that interfere with the renin angiotensin aldosterone system (RAAS) such as angiotensin receptor blockers and angiotensin converting enzyme (ACE) inhibitors. Other class effects include hyperplasia of renal juxtaglomerular cells (which is due to the compensatory response of increased renin production), decreased erythroid and reticulocyte parameters (due to blockade of angiotensin II- stimulated erythropoiesis), and decreased heart weights (directly related to hypotensive effect).

In the current submission, the incidence of juxtaglomerular hyperplasia was considerably higher in the HD combination group than in valsartan-only animals, suggesting a stronger renin compensatory response with combination dosing.

Erosions in the glandular stomach have previously been noted in toxicological studies of amlodipine with or without valsartan. These lesions are likely due to the combined exaggerated hypotensive effect of the combination that results in ischemia and hypoperfusion of the stomach.

Overall, the triple combination was well-tolerated in rat toxicity studies up to 13 weeks duration and the NOAEL was considered 0.5/8/1.25 mg/kg/day amlodipine/valsartan/HCT. The relative plasma exposure levels at the NOAEL in this bridging study were less than those anticipated clinically at the maximum clinical combination dose for each of the three components (Table 3). Similarly low exposure margins have been noted with each of the individual components alone in previous evaluations. The toxicities observed above the NOAEL were associated with exaggerated pharmacological effects of valsartan, HCT and/or amlodipine and reflect target organ toxicities which may be monitored in clinical practice. As there is already a great deal of postmarket experience with all three components of the combination used either individually or in various dual combinations, the current nonclinical data showing no novel toxicities suggest that there are no novel safety issues of clinical concern.

Genotoxicity, Carcinogenicity, Reproductive and developmental toxicity

No studies were submitted for the triple combination under these headings, which is acceptable and consistent with ICH guidelines for fixed dose combinations using previously approved components.[11] All three active substances have been approved and on the market for many years and there is extensive nonclinical and clinical information available. As noted in the proposed PI, Exforge HCT should not be used in pregnancy, consistent with the known effects of angiotensin receptor blockers in the second and third trimesters of pregnancy.

Paediatric use

Exforge HCT tablets are not intended for use in children.

Nonclinical Summary and Conclusions

The nonclinical data submitted in support of the safety of Exforge HCT tablets consisted of GLP-compliant bridging toxicology and toxicokinetic studies in rats of up to 13 weeks duration. This was an appropriate data package for a fixed combination of previously approved components.

Toxicokinetic data from the rat 13 week combination oral toxicity study revealed that all three compounds showed linear pharmacokinetics and rapid uptake into blood with T_{max} values of about 0.5-2 hours after dosing. Co-administration appeared to have little or no effect on exposure values for amlodipine, valsartan, and HCT, suggesting a lack of significant drug interaction. Relative plasma exposure levels (AUC) for each of the three combination components at the NOAEL of 0.5/8/1.25 mg/kg/day amlodipine/valsartan/HCT were less than those anticipated clinically at the maximum combination dose.

Metabolism, tissue distribution, and excretion studies were not performed. Published results indicate that amlodipine is converted to various metabolites and (in humans) is predominantly excreted in urine; valsartan is largely excreted unchanged via faeces; and HCT is largely excreted unchanged in urine.

Drug interaction studies were not performed. Published results indicate that amlodipine (which is metabolised by and also inhibits CYP3A4) can interact moderately with other drugs that are metabolised by CYP3A4. Both valsartan and HCT are known to undergo limited metabolism and

[11] http://www.emea.europa.eu/pdfs/human/ewp/024095en.pdf

show little inhibitory activity towards CYP enzymes, and hence are unlikely to interfere with CYP-mediated metabolism of other drugs.

Overall, the triple combination was well-tolerated in rat toxicity studies of up to 13 weeks duration and no novel toxicity was discerned. Target organ toxicities (reversible increases in serum creatinine and urea, renal juxtaglomerular hyperplasia, erosions in the glandular stomach, decreased heart weight, decreased erythroid parameters, decreased reticulocytes) were associated with exaggerated pharmacological effects of valsartan, HCT and/or amlodipine and were due to either blockade of the RAAS or organ hypoperfusion due to profound hypotensive effects. As there is already a great deal of postmarket experience with all three components of the combination used either individually or in various dual combinations, the current nonclinical data showing no novel toxicities suggest that there are no novel safety issues of clinical concern.

No genotoxicity, carcinogenicity, or reproductive toxicity studies were submitted for Exforge HCT, which is acceptable and consistent with ICH guidelines for fixed dose combinations using previously approved components. As noted in the PI, Exforge HCT should not be used in pregnancy due to the known effects of angiotensin receptor blockers in the second and third trimesters of pregnancy.

No significant pharmacokinetic interactions or novel toxicities were noted for the amlodipine/valsartan/HCT combination in a well conducted, GLP compliant, 13 week oral bridging toxicology study in rats.

The toxicities observed were well known reversible “class” effects and reflected target organ toxicities which can be monitored in clinical practice. Given that all three active substances have been approved and on the market for many years and that there is extensive nonclinical and clinical information available (for the individual components alone and in various dual combinations) there are no novel clinical safety concerns raised by the nonclinical data.

There are no objections to the registration of Exforge HCT tablets for the treatment of hypertension.

IV. Clinical Findings

Introduction

Overview of the clinical development program

The clinical development program consisted of 10 clinical studies, 9 of which were completed. Two completed studies were designed to assess the efficacy and safety of the valsartan / HCT / amlodipine combination ([VEA A2302] and [VEA ABR01]). VEAA2302 is the pivotal, multinational, double-blind, controlled study supporting the claim that valsartan/HCT/amlodipine is efficacious and safe in the treatment of hypertension and is the focus of the sponsor’s Clinical Overview. VEA ABR01 is a supportive, open-label, uncontrolled trial conducted in Brazil. One completed study (VAA A2201E), which was previously submitted in the Exforge submission, provides long-term efficacy and safety data in a group of patients not adequately controlled on valsartan/amlodipine who had open-label HCT added to their treatment regimen. The remaining six completed studies (VAA A2401, VAA A2402, VAA A2403, VAH BUS04, VAH BDE13E1, and VAH B2406E1) were designed to evaluate various regimens of either the amlodipine/valsartan, valsartan/HCT, or amlodipine/HCT dual combinations. They contain exposure to the triple combination through the double-blind or optional, open-label addition of the third component during the late phase of the study. The safety data in the subgroup of patients exposed to triple therapy from these studies are considered supportive. Efficacy data in this same group of patients were not summarized.

Rationale for this "triple" fixed combination

The active ingredients in Exforge HCT triple fixed combination: valsartan (angiotensin receptor blocker), HCT (diuretic), and amlodipine besylate (calcium channel blocker), are well established antihypertensive agents, which are commonly co-administered to treat hypertension.

Combination therapy in the treatment of hypertension as an appropriate treatment option is receiving broader acceptance amongst the clinical community. Monotherapy is often not sufficient to normalise blood pressure since the goal of treatment is to normalize both systolic and diastolic blood pressure. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has emphasised the importance of achieving blood pressure goals through aggressive treatment with multiple medications, if needed. Similar recommendations are made in the hypertension treatment guidelines recently issued by the European Society of Hypertension and European Society of Cardiology or, in the Guide to Management of Hypertension 2008 issued by the Australian Heart Foundation.

An estimated 50-75% of patients with hypertension will not achieve BP targets with monotherapy (The Heart Foundation Guide to Management of Hypertension 2008). For most patients, a combination of hypertensive drugs from two or more pharmacological classes is needed. Occasionally a combination of more than three antihypertensive drugs may be required to achieve adequate BP control. Data from pivotal clinical studies already evaluated by the TGA show that:

(i) 18 to 30% of hypertensive patients do not achieve adequate BP control on Exforge 5/160 or 10/160 mg and that,

(ii) 20 to 26% of hypertensive patients do not achieve adequate BP control on Co-Diovan 160/12.5, 320/12.5 or 320/25 mg.

Justification for the combination of agents

The combination of an angiotensin receptor blocker (ARB), calcium channel blocker (CCB), and diuretic is a rational therapeutic option because:

- The mechanisms of action of the three drugs are complementary.
- Well-known side effects of the individual drugs may be mitigated by adding a complementary agent (for example, ARB that spares potassium from being excreted renally), or by using a complementary agent rather than increasing the dose of a single agent.
- The triple fixed-dose combination of amlodipine, valsartan and HCT is expected to provide a convenient single once daily tablet for patients who require all three components to achieve the recommended blood pressure control, and to improve therapeutic compliance over the drugs administered separately.

Compliance and simplification of dose

Poor patient compliance can lead to hospital admissions and disease progression. Research suggests that simplification of complex dose regimens can help improve patient compliance and outcomes.[12] An estimated 50–75% of patients with hypertension will not achieve BP targets with monotherapy. For most patients, a combination of antihypertensive drugs from two or more pharmacological classes is needed. For these patients, the triple combination represents a significant simplification of dose and a potential for improved compliance.

[12] Neutel JM, Smith JHD. Improving patient compliance: a major goal in the management of hypertension. J Clin Hypertension 2003; 5: 127-132.

Dose/strength selection

The doses selected in the studies included in this submission, that is, valsartan (80, 160 and 320 mg once daily [od]) in combination with amlodipine (2.5, 5, or 10 mg od) and HCT (12.5 or 25 mg od) were based on the available marketed strengths of the three drugs. No specific dose selection studies were conducted. In the pivotal efficacy trial (Study 2302) maximum doses of amlodipine/valsartan/HCT 10/320/25 mg, were compared with maximum doses of the dual combinations (valsartan/HCT 320/25 mg, amlodipine/valsartan 10/320 mg, and HCT/amlodipine 25/10 mg). Study VEA ABR01 is the only dose selection study in the submission, in which patients received therapy with valsartan/HCT 160/12.5 mg for 4 weeks followed by an additional 4 weeks of treatment with valsartan /HCT /amlodipine 160/12.5/5 mg. However, this study was run in Brazil exclusively, involved 326 patients and assessed lower doses only. There is no dose selection in Study VAA A2201E1 which was assessing the efficacy of the dual therapy in 1300 patients and the number of patients who received triple therapy was 271.

It should be noted that in the EU guideline, *Second-line therapy of the Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, CPMP/EWP/238/95 Rev.2*, the importance of dose finding studies is emphasised. In the *Addendum for Fixed Combination Antihypertensive Medicinal Products* in *Second Line Therapy, Issue 3*, it is further stated that "at least one add-on trial to active treatment in non-responders should be carried out". Considering the EU guideline, the strength of dose finding studies submitted with this application is insufficient. However, there are no clear guidelines for assessing efficacy of a triple combination as add-on therapy to all possible dual therapy options in management of hypertension.

Pharmacodynamics

Overview

Studies specifically designed to evaluate the pharmacodynamics of the fixed combination of valsartan/ HCT (HCT)/amlodipine were not performed. However, a single study in 297 patients with mild to moderate essential hypertension examined the efficacy of valsartan in fasted and fed subjects.

Pharmacodynamics in the target population

A double-blind, randomised, placebo-controlled, parallel design trial (Study No: VAL489A0017) of 12 to 14 weeks duration examined the effect of food on the antihypertensive response of valsartan in 297 patients (118 female), aged from 22 to 75 years, with mild to moderate essential hypertension. Fifty nine subjects were allocated to the placebo group, 120 to the valsartan fasted group and 118 to the valsartan fed group. Patients had a mean sitting diastolic blood pressure (msDBP) of ≥ 100 mmHg and ≤ 114 mmHg at the end of the placebo run-in period. The trial consisted of a 2-week medication-free period followed by a single-blind placebo run-in lasting from 2 to 4-weeks. Subsequently, the double-blind portion of the trial consisted of an 8 week treatment period with patients receiving 80 mg valsartan or placebo in a fasted or fed state. Two hundred and fifty six subjects completed the trial. The primary efficacy variable examined the change from baseline in trough msDBP, 24 to 26 hours post-dosing comparing: 80 mg valsartan versus placebo; and 80 mg valsartan fed versus fasted. Valsartan 80 mg, in both fasted and fed groups, was significantly superior at reducing trough mean DBP both at end point and at Visit 7 (treatment week 12). In addition, at both the study endpoint and Visit 7, there was no difference between the antihypertensive response in the fasted and fed groups, although it approached significance at the 0.05 level (0.082 and 0.078, respectively). This may in part reflect the large variability in plasma trough levels of valsartan seen under fed and fasted conditions.

Pharmacokinetics

Overview

Nine human studies, comprising 275 subjects (164 healthy and 111 patients with hypertension), examined the pharmacokinetics of Exforge HCT.

Coupled high pressure liquid chromatography-mass spectrometry (HPLC-MS/MS) was used for the simultaneous quantitative determination of HCT, amlodipine and valsartan in human plasma. The method was suitable for the routine analysis within the range of 1.00 ng/mL to 200 ng/mL for HCT, 0.0250 ng/mL to 10.0 ng/mL for amlodipine, 5.00 ng/mL to 10000 ng/mL for valsartan using 100 µl human plasma.

Absorption, distribution and elimination

No information regarding the absorption, distribution and elimination of Exforge HCT was provided in the submission, however, the profile of each individual drug in the proposed combination is well established.

Bioequivalence

Study A2305

This was an open-label, randomised, single dose, four period, crossover study which examined the relative bioavailability of three prototype 160/12.5/5 mg fixed combination valsartan/HCT/amlodipine tablets to a free combination of the Phase III-clinical trial presentations (CTPs) of 160 mg valsartan, 12.5 mg HCT, and 5 mg amlodipine. Thirty two healthy subjects (9 female), aged 20 to 43 years, were enrolled and 26 subjects completed the study. All 32 subjects were included in the safety analysis and all subjects who received any treatment and had evaluable PK data for that treatment were included in the PK data analysis. Subjects were randomly assigned (8 per group) to 1 of 4 treatment sequences (ABCD, BDAC, CADB, and DCBA) and received 4 single doses of the assigned study treatment, each separated by a 14-day washout period:

Treatment A: Single dose of 160/12.5/5 mg fixed combination valsartan/HCT/amlodipine tablet (prototype I) (investigational drug);

Treatment B: Single dose of 160/12.5/5 mg fixed combination valsartan/HCT/amlodipine tablet (prototype II) (investigational drug);

Treatment C: Single dose of 160/12.5/5 mg fixed combination valsartan/HCT/amlodipine tablet (prototype III) (investigational drug); and

Treatment D: Single dose of free combination of CTPs

Subjects were treated under fasting conditions and sample collection for pharmacokinetic assessments were taken pre-dose and up until 168 hours post-dose. The pharmacokinetics of valsartan were similar for all 4 treatments with AUC_{0-t} and C_{max} ranging from 26019 - 27781 ng.h/ml and 3366 - 3911 ng/ml respectively (Table 4). The pharmacokinetics for HCT were similar for all 4 treatments with AUC_{0-t} and C_{max} ranging from 476.8 - 519.9 ng.h/ml and 73.1 - 82.9 ng/ml respectively (Table 5). The pharmacokinetics for amlodipine were similar for all 4 treatments with AUC_{0-t} and C_{max} ranging from 127.5 - 137 ng.h/ml and 2.6 - 2.8 ng/ml respectively (Table 6). The HCT and amlodipine pharmacokinetics for the three prototype formulations are similar to and bioequivalent with the CTP free combination (Table 1, Section II). For valsartan pharmacokinetics, although prototype formulation I is bioequivalent to the CTP free combination, the AUC_{0-t}s of Prototype II and III are slightly higher (upper bounds of the 90% CIs are 1.28 and 1.32, respectively).

Table 4: Study No. VEA489A2305 – PK Data for valsartan

Mean plus/minus SD (CV%) Pharmacokinetic parameters of valsartan following a single dose of 160/12.5/5 mg valsartan/HCTZ/amlodipine fixed combination tablet (prototype I, II and III) or free combination CSFs of 160 mg valsartan, 12.5 HCTZ and 5 mg amlodipine

Parameter	Treatment			
	Prototype I (n = 29)	Prototype II (n = 26)	Prototype III (n = 28)	Free Combination (n = 27)
$AUC_{0-\infty}$ (ng.h/mL)	26327 ± 10952[a] (42%)	28163 ± 9541 (34%)	29146 ± 10134[b] (35%)	26610 ± 13192 (50%)
AUC_{0-t} (ng.h/mL)	26019 ± 10822 (42%)	27781 ± 9581 (35%)	27465 ± 9772 (36%)	26355 ± 13180 (50%)
C_{max} (ng/mL)	3525 ± 1529 (43%)	3911 ± 1174 (30%)	3366 ± 1259 (37%)	3569 ± 1729 (49%)
t_{max} (hr) Median (min, max) (CV%)	3.0 (1.0-4.0) (39%)	3.0 (1.0-4.1) (40%)	3.0 (1.0-10.0) (48%)	3.0 (1.0-4.1) (34%)
$t_{1/2}$ (hr)	18.3 ± 12.4[a] (68%)	21.7 ± 20.8 (96%)	23.4 ± 27.2[b] (116%)	15.4 ± 5.7 (37%)

[a]n = 28; [b]n = 24.

Table 5: Study No. VEA489A2305 – PK Data for HCT

Mean plus/minus SD (CV%) Pharmacokinetic parameters of HCTZ following a single dose of 160/12.5/5 mg valsartan/HCTZ/amlodipine fixed combination tablet (prototype I, II and III) or free combination CSFs of 160 mg valsartan, 12.5 HCTZ and 5 mg amlodipine

Parameter	Treatment			
	Prototype I (n=30)	Prototype II (n=27)	Prototype III (n=29)	Free Combination (n=28)
$AUC_{0-\infty}$ (ng.h/mL)	517.6 ± 125.5 (24%)	542.1 ± 123.0 (23%)	522.8 ± 156.6 (30%)	516.4 ± 143.1[a] (28%)
AUC_{0-t} (ng.h/mL)	496.0 ± 125.3 (25%)	519.9 ± 123.3 (24%)	500.3 ± 154.2 (31%)	476.8 ± 169.5 (36%)
C_{max} (ng/mL)	76.3 ± 21.7 (28%)	82.9 ± 23.8 (29%)	75.8 ± 24.0 (32%)	73.1 ± 25.5 (35%)
t_{max} (hr) Median (min, max) (CV%)	2.0 (1.0-4.0) (52%)	1.0 (1.0-3.0) (45%)	2.0 (1.0-8.0) (74%)	2.0 (1.0-4.0) (40%)
$t_{1/2}$ (hr)	9.5 ± 1.8 (19%)	9.9 ± 1.7 (17%)	9.6 ± 1.4 (14%)	10.0 ± 1.2[a] (12%)

[a]n = 27

Table 6: Study No. VEA489A2305 – PK Data for Amlodipine

Mean plus/minus SD (CV%) Pharmacokinetic parameters of amlodipine following a single dose of 160/12.5/5 mg valsartan/HCTZ/amlodipine fixed combination tablet (prototype I, II and III) or free combination CSFs of 160 mg valsartan, 12.5 HCTZ and 5 mg amlodipine

Parameter	Treatment			
	Prototype I (n=29)	Prototype II (n=27)	Prototype III (n=28)	Free Combination (n=27)
$AUC_{0-\infty}$ (ng.h/mL)	143.4 ± 45.5 (32%)	139.5 ± 45.1 (32%)	148.5 ± 46.3 (31%)	142.2 ± 50.6 (36%)
AUC_{0-t} (ng.h/mL)	130.6 ± 38.8 (30%)	127.5 ± 39.2 (31%)	137.0 ± 39.7 (29%)	130.9 ± 43.3 (33%)
C_{max} (ng/mL)	2.7 ± 0.6 (21%)	2.6 ± 0.7 (26%)	2.8 ± 0.6 (23%)	2.7 ± 0.7 (26%)
t_{max} (hr) Median (min, max) (CV%)	6.0 (6.0-12.1) (25%)	6.0 (6.0-12.2) (22%)	6.0 (6.0-16.0) (30%)	6.0 (3.0-12.0) (29%)
$t_{1/2}$ (hr)	45.1 ± 9.0 (20%)	46.8 ± 13.3 (28%)	43.2 ± 9.0 (20%)	43.4 ± 8.0 (18%)

Study A2106

This was an open label, randomised, single-dose, two-way crossover study which examined the bioequivalence of the amlodipine component between the fixed combination of 160/25/10 mg valsartan/HCT/amlodipine proposed marketing formulation tablet and the 10 mg amlodipine tablet (Istin) administered in combination with 160 mg valsartan and 25 mg HCT tablets in 26 healthy male subjects with an average (±SD [standard deviation]) age of 25.8 ± 7.83 years. Each subject participated in a 21-day screening period, 2 baseline and treatment periods and an end of study evaluation. Subjects were randomly assigned to 1 of 2 treatment sequences (AB or BA) and each received 2 single oral doses of the assigned study treatment separated by a 14-day washout period. Treatment A comprised a single dose of the triple combination tablet of 160 mg valsartan / 25 mg HCT/10mg amlodipine, whereas treatment B comprised a single dose of the free combination of 160 mg valsartan, 25mg HCT, and 10 mg amlodipine (Istin) tablets. Three subjects were withdrawn from the study: one subject violated the diet restrictions during the washout period and two subjects had abnormal safety laboratory results. The T_{max}, C_{max} and AUC of amlodipine were similar for both formulations and the amlodipine component of 160/25/10 mg valsartan/HCT/amlodipine is bioequivalent to 10 mg of amlodipine tablet (Istin) administered as a free combination with 160 mg valsartan and 25 mg HCT tablets.

Study A2306

This was an open-label, randomised, single dose, three period, crossover study which examined the relative bioavailability of two prototype 160/25/10 mg fixed combination valsartan/HCT/amlodipine tablets to a free combination of 160 mg valsartan, 25 mg HCT, and 10 mg amlodipine. Thirty healthy subjects (1 female), aged 19 to 44, were enrolled and 28 subjects completed the study requirements. All 30 subjects were included in the safety analysis. All subjects with at least one evaluable PK parameter were included in the PK data analysis. Subjects were randomly assigned (10 per group) to 1 of 3 treatment sequences (ABC, BCA, or CAB) and each received 3 single oral doses of the assigned study treatment each separated by a 14-day washout period:

Treatment A: Single dose of 160/25/10-mg fixed-combination valsartan/HCT/amlodipine tablet (prototype I) (investigational drug);

Treatment B: Single dose of 160/25/10-mg fixed-combination valsartan/HCT/amlodipine tablet (prototype II) (investigational drug); and

Treatment C: Single dose of free combination of 160-mg valsartan, 25-mg HCT, and 10-mg amlodipine tablet (free combination) (reference treatment).

The valsartan pharmacokinetics were similar for all three formulations with AUC_{0-t} and C_{max} ranging from 32.6 - 34.7 μg.h/ml and 5.0 - 5.5 μg/ml, respectively. The HCT pharmacokinetics were similar for all three formulations with AUC_{0-t} and C_{max} ranging from 1005 - 1026 μg.h/ml and 153.5 - 156 μg/ml, respectively. The amlodipine pharmacokinetics were also similar for all three formulations with AUC_{0-t} and C_{max} ranging from 293 - 310 μg.h/ml and 5.5 - 5.7 μg/ml, respectively. Both prototype formulations were bioequivalent with the free combination formulation (90% CIs for AUC_{0-t} and C_{max} ranged from 0.85 - 1.19 and 0.97 - 1.17, respectively (Table 2, Section II).

Bioavailability Studies

Effect of food on valsartan PK

An open, single dose, single centre, two-way balanced cross-over trial (Study No: VEA489A 0006) examined the effects of food on the pharmacokinetics of valsartan in 12 male subjects aged 22 to 44 years. Subjects were randomly assigned to one of two treatment sequences AB or BA and there was a 14-day wash-out between the treatment periods. Treatment A comprised of a single 160 mg oral dose of valsartan following an overnight fast of at least 12 hours, whereas treatment B comprised a single 160 mg oral dose of valsartan taken immediately after a standard American breakfast as defined by the FDA. Compared to the fasted condition, food decreased the AUC_{0-24} of valsartan (mean ± SD = 50 ± 19.4 and 29 ± 11.9 μmol.h/l, on fasted and fed conditions respectively) and drug absorption decreased by approximately 50% in the fed state. The rate of absorption was also decreased as T_{max} increased and C_{max} decreased when valsartan was administered with food. Median T_{max} was 6 hours post dosing for fed compared to 2.5 hours for the fasted treatment. The corresponding C_{max} values were 3.89 ± 1.38 μmol/ml and 8.26 ± 2.63 μmol/ml for fed and fasted subjects, respectively. By contrast the fed and fasted half lives were similar for both groups (5.3 ± 2.0 and 5.6 ± 1.5 hours, respectively). Overall, food appears to reduce the rate and extent of valsartan absorption.

Effect of food on the bioavailability of valsartan/HCT/amlodipine

The effect of food on the bioavailability of valsartan/HCT/amlodipine 320/25/10 mg fixed combination tablet proposed for marketing was examined in a randomised, open-label, single-dose, two-period crossover study (Study no. VEA489A2310) in 36 healthy subjects (1 female) aged from 18 to 45 years with body mass indices (BMIs) ranging from 18.7 to 29.8 kg/m^2. Thirty three subjects completed all study procedures and treatments according to the protocol. Three subjects discontinued study participation prematurely (due to withdrawn consent, asymptomatic hypotension or abnormal lab values after period 1) and these subjects were not replaced. All 36 subjects were included in the safety and pharmacokinetic analysis. Single oral doses of the investigational drug, 320/25/10 mg of valsartan/HCT/amlodipine tablets were administered under fed or fasted conditions. The duration of treatment was 23 days (single dose in each of two treatment periods, with at least a 14-day washout between doses). Although the upper bounds of the confidence intervals for C_{max} and AUC_{0-t} were slightly high (1.29 and 1.31 respectively) for valsartan (Table 7), on the whole the statistical summary comparing the pharmacokinetic results under fed and fasted conditions were similar. Hence, the bioavailabilities of valsartan, HCT and amlodipine were similar under both fed and fasted conditions (C_{max} and AUC_{0-t} fell within the 0.80 - 1.20).

Table 7: Study no. VEA489A2310 – Summary ok PK under Fed and fasted Conditions

Statistical summary for PK parameters of valsartan, hydrochlorothiazide, and amlodipine following a single oral dose administration of 320/25//10 mg valsartan/hydrochlorothiazide/ amlodipine fixed combination tablet under fed and fasting conditions

	Geometric mean		Geometric mean ratio	
	Fed (n=35)	Fasting (n=35)	Estimate	90% CI
			Valsartan	
C_{max} (ng/mL)	5327.61	4739.52	1.12	0.98 - 1.29
AUC_{0-t} (hr*ng/mL)	46645.61	40982.76	1.14	0.99 - 1.31
$AUC_{0-\infty}$ (hr*ng/mL)	47199.80	41429.90	1.14	0.99 -1.31
			Hydrochlorothiazide	
C_{max} (ng/mL)	110.72	128.60	0.86	0.79 – 0.93
AUC_{0-t} (hr*ng/mL)	1031.83	940.63	1.10	1.02 – 1.18
$AUC_{0-\infty}$ (hr*ng/mL)	1064.98	980.53	1.09	1.02 – 1.16
			Amlodipine	
C_{max} (ng/mL)	4.64	4.18	1.11	1.05 – 1.18
AUC_{0-t} (hr*ng/mL)	208.65	191.96	1.09	1.03 – 1.15
$AUC_{0-\infty}$ (hr*ng/mL)	228.31	208.89	1.09	1.04 – 1.15

Effect of over encapsulation on the PK of amlodipine

An open label, randomised, single-dose, two-way crossover study (Study No: VEA489A 2105) examined the bioavailability of 5 mg amlodipine CTP capsule relative to that of the 5 mg amlodipine administered as one 5 mg Norvasc tablet in twenty four healthy male subjects aged from 18 to 42 years. This study was conducted to assess the effect of over encapsulation on the

bioavailability of amlodipine. Each subject participated in a 21-day screening period, two baseline and treatment periods with a washout period of at least 14 days between two treatment periods (A and B) and an end-of study evaluation. Treatment A consisted of a single 5 mg dose of amlodipine CTP-over encapsulated and treatment B consisted of a single 5 mg dose of amlodipine administered as one 5 mg marketed amlodipine tablet (Norvasc). Subjects were randomised in equal numbers to one of the two treatment sequences ie AB or BA. The $T_{max,}$ $C_{max,}$ AUC and $t_{1/2}$ were similar for both the CTP capsule and the marketed formulation. The rate (C_{max}) and extent (AUC) of absorption of amlodipine were bioequivalent for the 5 mg amlodipine CTP capsule and the 5 mg amlodipine marketed tablet, suggesting that over encapsulation does not affect the bioavailability of amlodipine.

Pharmacokinetics in the target population

A multi-centre, multiple dose, open-label, four-cohort, parallel study (Study No: VEA489A2104) examined the pharmacokinetic drug interactions following co-administration of valsartan, HCT and amlodipine in 111 patients (32 female) with hypertension aged from 21 – 59 years. Patients were randomised and allocated to one of the cohorts described in Table 8. One hundred and one patients completed the study.

Table 8: Study No: VEA489A2104 – Dosing Scheme

Treatment cohorts and dosing schema

		Days		
Cohort	Treatment pattern	Days 1–6 (dose titration phase)	Days 7 – 17 (highest dose treatment phase)	Day 17 (PK phase)
Cohort 1	(V/H)	V/H 160/12.5 mg	V/H 320/25 mg	PK of V and H for 24 hrs
Cohort 2	(V/A)	V/A 160/5 mg	V/A 320/10 mg	PK of V and A for 24 hrs
Cohort 3	(H/A)	H/A 12.5/5 mg	H/A 25/10 mg	PK of H and A for 24 hrs
Cohort 4	(V/H/A)	V/H/A 160/12.5/5	V/H/A 320/25/10 mg	PK of V, H & A for 24 hrs

The treatments are as follows: V = Valsartan; H = HCTZ; A = Amlodipine; PK = Pharmacokinetic

Co-administration of valsartan increased the AUC of HCT by 8% and decreased its C_{max} by 17%, whereas, it induced a 9 to 10% increase in the AUC and C_{max} of amlodipine.

HCT increased the AUC and the maximal plasma concentration at steady state (Css_{max}) of valsartan by 25% and,22%, respectively, whereas, it increased the AUC and Css_{max} of amlodipine by approximately 10%.

Amlodipine increased the AUC and Css_{max} of valsartan by 10% and 15%, respectively, and induced small increases (2-3%) in AUC and Css_{max} of HCT.

Valsartan, therefore, is unlikely to have any clinically relevant effects on the pharmacokinetics of HCT and amlodipine and although valsartan exposure increased by 10% to 25% when co-administered with HCT and amlodipine, this increase was lower than the total variability of valsartan exposure and is unlikely to be clinically relevant.

Drug interaction studies

Studies have been conducted with the individual amlodipine, valsartan and HCT components, however, no studies were conducted to examine the drug interaction between Exforge HCT and other drugs likely to be used in the target patient population.

Valsartan with HCT

An open label, single dose, single centre, 3-way balanced cross-over trial (Study No: VEA489A) examined whether the co-administration of valsartan with HCT alters the pharmacokinetics of valsartan or HCT in 12 healthy male volunteers aged from 18 to 37 years. Each subject was assigned to one of six treatment sequences and received one dose each of 160 mg valsartan (Treatment A), 25 mg HCT (Treatment B) and 160 mg valsartan in combination with 25 mg HCT (Treatment C). The three open-label treatment periods were separated by a 14 day wash-out between each period. The AUC_{0-24} (mean ± SD) for valsartan for treatment A (valsartan alone) and treatment C (valsartan + HCT) were 55.7 ± 22.1 h.µmol/l and 48.5 ± 22.2 h.µmol/l, respectively. The half life and elimination constant rate for treatment A and treatment C were similar and ranged from 6.47 - 6.59 hours and 0.106 - 0.127 l/hours, respectively. The AUC_{0-24} for HCT for treatment B (HCT alone) and treatment C (valsartan + HCT) were 3030 ± 693 h.nmol/l and 2370 ± 712 h.nmol/l, respectively. The half life and elimination constant rate for treatment B were 12.4 ± 4.14 hours and 0.064 ± 0.027 l/h , respectively and for treatment C were 8.13 ± 1.69 hours and 0.090 ± 23 l/h, respectively. HCT decreased the $AUC_{(0-\infty)}$ and C_{max} of valsartan by 13 and 19% respectively whereas it increased the elimination rate 11%, however these differences were not significant. By contrast, valsartan significantly decreased the AUC and C_{max} of HCT by 31% and 26% respectively and significantly increased the elimination rate by 46%, whereas, although the amount of HCT excreted in the urine (Ae) decreased (14%) this result did not reach significance.

Valsartan and amlodipine

The pharmacokinetic interaction between valsartan and amlodipine following single doses of both drugs was examined in a single centre, randomised, open-label, three-way cross over study (Study No: VEA489A 0037) in 12 healthy male subjects aged 20 to 46 years. There was a two to three week wash-out between doses. Each subject received the following treatments: treatment A, 160 mg valsartan; treatment B, 5 mg amlodipine; and treatment C, 160 mg valsartan in combination with 5 mg amlodipine. Amlodipine did not significantly effect the AUC of valsartan and the AUC values in the presence and absence of amlodipine were bioequivalent (90% CI: 0.81 - 1.17). By contrast, the C_{max} of valsartan was lower in the presence of amlodipine (90% CI: 0.69 - 1.04) but the study's authors argue this is unlikely to be clinically significant as the inter-subject co-efficient of variation for valsartan C_{max} was high (44 - 69%) and this may explain this difference. Valsartan had little effect on the pharmacokinetics of amlodipine and the AUC and C_{max} of amlodipine in the presence and absence of valsartan were bioequivalent (90% CI ranged from 0.96 - 1.16).

Pharmacokinetics in Special Groups

No studies examined the pharmacokinetics of Exforge HCT in special populations of subjects such as the elderly or subjects with hepatic or renal dysfunction.

Summary of the Pharmacokinetic Studies

Following oral administration of the fixed combination of valsartan/HCT/amlodipine under fasted conditions, peak plasma concentrations of valsartan, HCT and amlodipine were obtained in 3-4, 1-3 and 6-9 hours, respectively. The elimination half-lives of valsartan, HCT and amlodipine were approximately 13-23, 10-12, 41-47 hours, respectively.

The rate and extent of absorption of the fixed combination of valsartan/HCT/amlodipine were equivalent to the bioavailability of valsartan, HCT and amlodipine when administered as individual tablets.

Although there is evidence that valsartan decreases the exposure of HCT by up to 31%, in general there is an absence of drug interaction when the drugs are administered as dual combinations (valsartan and HCT; valsartan and amlodipine) versus the corresponding mono components. It must be noted that no pharmacokinetic data were provided for the co-administration of amlodipine

with HCT, however an interaction is believed to be less likely based on the two drug's pharmacokinetic characteristics, which are: the peak plasma concentrations of amlodipine occurs between 6-9 hr following oral administration, and amlodipine is primarily eliminated through hepatic metabolism; whereas, the peak plasma concentrations of HCT occurs between 1-3 hours following oral administration, and HCT is renally eliminated as unchanged drug.

Efficacy

Overview

The clinical development program consisted of 10 clinical studies, 9 of which are completed. Two completed studies were designed to assess the efficacy of the valsartan/HCT/amlodipine combination (VEA A2302 and VEA ABR01. One completed study, VAA A2201E provides evidence for long-term efficacy and safety. The remaining six completed studies (VAA A2401, VAA A2402, VAA A2403, VAH BUS04, VAH BDE13E1, and VAH B2406E1) were designed to evaluate various regimens of either the amlodipine/valsartan, valsartan/HCT, or amlodipine/HCT dual combinations. These studies do not contain evaluable data concerning the efficacy of the triple combination. It is unclear as to why these studies have been included in the submission.

Pivotal Study VEA A2302

Study Design and Patient Characteristics

Study VEA A2302 was a large pivotal, double blind, positive controlled study conducted at 273 sites in 15 countries (Argentina, Canada, Denmark, Ecuador, Greece, Hong Kong, Norway, Peru, Portugal, Russia, Sweden, Turkey, UK, US, Venezuela). Since combination therapy is required more often in patients with more severe hypertension to achieve appropriate BP control, this study examined the efficacy and safety of the valsartan/HCT/amlodipine triple combination versus dual combinations in patients with moderate to severe hypertension (MSDBP $\geq$ 100 mmHg and <120 mmHg and mean sitting systolic blood pressure [MSSBP] $\geq$ 145 mmHg and <200 mmHg). This trial was designed to evaluate the efficacy and safety of once-daily treatment with the combination of valsartan/HCT/amlodipine 320/25/10 mg compared to 3 dual therapies: valsartan/HCT 320/25 mg, valsartan/amlodipine 320/10 mg, and HCT/amlodipine 25/10 mg.

A single-blind run-in period of up to 4 weeks was followed by an 8-week double-blind treatment period. Maximum duration of an individual patient's participation, including washout, was 13 weeks (Table 9). A total of 2024 patients (506 patients per treatment group) were randomized in a double-blind fashion for a total of 8 weeks of treatment in an equal allocation (1:1:1:1) to one of four treatment arms:

- Valsartan/HCT/amlodipine: 320/25/10 mg od
- Valsartan/HCT: 320/25 mg od
- Valsartan/amlodipine: 320/10 mg od
- HCT/amlodipine: 25/10 mg od

The comparator arms in this study represent one combination product that is marketed (Diovan HCT), another combination product that was pending approval at the time the protocol was developed (Exforge), and the third combination, HCT/amlodipine, which is not available as a combination product.

The superiority of the triple combination to all 3 dual combinations had to be demonstrated to ensure that each component contributes to the overall antihypertensive effect.

Approximately 4500 patients were expected to be screened for entry into the single-blind run-in period, 2252 patients (563 randomized patients per treatment group) were expected to be randomized, and 2024 patients (506 patients per treatment group) were expected to complete the

trial. Planned enrolment in the ambulatory blood pressure monitoring (ABPM) sub study was for 670 randomized and 506 completed patients at selected study centres.

Table 9: VEA A2302 Study design outline

Phase	Pre-randomization		Study Drug Treatment					
Period	Single-blind run-in1		Double-blind treatment					
Duration	(1-2 weeks)	(1-3 weeks)	(8 weeks)					
Visit	1	2	3	4	5	6	7	8
Week	-4	-2	1	2	3	5	7	9
Treatment	Placebo		Randomization					
			V/H/A2	V/H/A3	V/H/A4			
			0/12.5/5	0/12.5/5	0/25/10			
			160/12.5/0	160/12.5/0	320/25/0			
			160/0/5	160/0/5	320/0/10			
			160/12.5/0	160/12.5/5	320/25/10			

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

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

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

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

Patients had to meet the following criteria for inclusion into the study:

1. Male or female patients ≥ 18 years and <86 years of age
2. Diastolic and systolic blood pressure requirements:
   - Diagnosis of moderate to severe hypertension (MSDBP ≥ 100 mmHg and <120mmHg, and MSSBP ≥ 145 mmHg and <200 mmHg) at Visit 3
   - Patients also had to meet the blood pressure requirements (MSDBP ≥ 95 mmHg and <110 mmHg, and MSSBP <180 mmHg) at Visit 2

   or

   - MSDBP ≥ 110 mmHg and <120 mmHg, and MSSBP ≥ 145 mmHg and <200 mmHg, or MSDBP ≥ 100 mmHg and <110 mmHg and MSSBP ≥ 180 mmHg and <200 mmHg after one week of treatment with placebo (blood pressure check) or at any subsequent scheduled study visit or blood pressure evaluation during the single-blind run-in period (designated Visit 3)
3. Written informed consent to participate in the study prior to any study procedures.
4. Ability to communicate and comply with all study requirements.

Comment : This was a parallel group study of the high dose triple combination, 320/25/10 compared with all three possible dual combinations, that is, 320/25, 320/10 and 25/10. There have been no studies of add-on therapy and dose titration of the third drug (in accordance with section

7.2, *Second-line therapy of the Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, CPMP/EWP/238/95 Rev.2*). Furthermore, there have been no studies, either parallel or add-on, of any of the proposed lower strength triple combinations. In the absence of EU guidelines referring to triple therapy an attempt should be made to extrapolate the requirements referring to dual combinations to the triple combinations. Considering that patients being prescribed triple therapy will have already been on the highest dose of the dual combination, a dose selection study would be recommended for the third add-on component only.

Patient selection criteria were chosen based on the known safety profiles of angiotensin receptor blockers, HCT and calcium channel blockers, and the need to avoid confounding factors that could influence the primary efficacy variable. Accordingly, patients with renal-, hepatic- and cardiac-failure, diabetics or malignant hypertensives with encephalopathy or cerebrovascular accident have been excluded. This represents a target population somewhat different from that encountered in the daily clinical practice.

Efficacy Endpoints and Statistical Considerations

The primary efficacy variables were the changes from baseline to endpoint in MSDBP and in MSSBP.

The primary efficacy analysis was evaluated in the pre-specified intent-to-treat (ITT) population. All randomized patients with at least one post-baseline blood pressure assessment were included in the ITT population.

The focus of this efficacy summary is MSDBP, MSSBP, control rate, responder rate as well as ambulatory diastolic BP (ADBP) and ambulatory systolic BP (ASBP). The primary hypothesis investigated was whether triple combination therapy was more efficacious than the dual combination therapy components. Hochberg adjustment was applied to multiple comparisons for the two blood pressures.

The change from baseline in MSDBP and MSSBP at endpoint was analysed using an analysis of covariance model. For control rate and responder rate, a logistic regression model was used.

The change from baseline in post-dosing 24-hour mean ADBP and ASBP was analysed using a repeated measures model. The change from baseline in daytime and night-time mean ADBP and ASBP was analysed using an analysis of covariance model for repeated measures.

It was planned to obtain 2024 completed patients (506 patients per arm). Assuming a maximum dropout rate of 10%, a total of 2252 patients were planned to be randomized into the four treatment groups (563 patients per arm). The planned sample size of 506 completed patients (563 randomized patients) per treatment group would provide 90% power to obtain statistical significance for the triple versus all three dual therapies at the two-sided significance level of 0.025 for change from baseline in MSDBP, assuming the true treatment difference is 2 mmHg between the triple and each dual therapy and a common standard deviation of 8 mmHg for all treatment groups. This sample size would also provide 90% power to obtain statistical significance for the triple versus all three dual therapies at the two sided significance level of 0.025 for change from baseline in MSSBP, assuming the true treatment difference is 3.5 mmHg between the triple and each dual therapy and a common standard deviation of 14 mmHg for all treatment groups. The correlation structure among the three test statistics (corresponding to the three comparisons) was incorporated in the algorithm of power calculation for sample size estimation. Assuming the above magnitudes for the treatment differences in MSDBP and MSSBP, the probability to achieve the primary objective of the study (at least one success from MSDBP and MSSBP) would be at least 90%.

Patient disposition and baseline characteristics

A total of 4285 patients were enrolled into the single-blind period of the study. A total of 2272 patients completed the single-blind period; 2013 were discontinued. The most common reason for

discontinuation from the single-blind period was subject condition no longer required study drug (1204 patients; 28.1%). This reason for discontinuation included patients who did not meet the blood pressure criteria for randomization. Other frequently reported reasons for discontinuation were abnormal test procedure results (295 patients; 6.9%) and withdrawal of consent (228 patients; 5.3%).

Of the total randomized population, 312 patients (13.7%) had protocol deviations that excluded them from the Per Protocol population. The most frequently occurring deviations (as reported in the triple therapy group) were time of BP measurement <20 or >30 hours post last dose of study medication, study drug interruption >3 consecutive days prior to Visit 8/End of Study, and use of NSAIDs and/or Cox-2 inhibitors ≤72 hours prior to Visits 3 or 8/End of Study. Other frequently reported deviations (in the total randomized population) were patients randomized with a MSDBP <95 mmHg at Visit 2, and patients randomized with MSSBP ≥145 and <180 mmHg and MSDBP ≥100 and <110 without having a Visit 2.

The majority of patients were Caucasian (71.6%), male (55.3%) with a mean age of 53.2 years (only 14% being 65 years of age or older and 1.8% being 75 years of age and older). The treatment groups were generally comparable with respect to the demographic characteristics. The treatment groups were also comparable with regard to baseline disease characteristics. Mean sitting blood pressure was 169.9/106.5mmHg. The overall mean duration of hypertension was approximately 9 years. Diabetics comprised 9.5% of the randomized population.

Primary efficacy results

At endpoint, a clinically and statistically significant greater reduction of 24.6 mmHg in MSDBP was achieved with triple therapy, compared to reductions of 19.5 to 21.5 mmHg with the 3 dual combination treatments (p<0.0001). For MSSBP, a significantly greater reduction of 39.4 mmHg was achieved with triple therapy, compared to 31.5 – 33.5 mmHg with dual combination treatment (p<0.0001) (Table 10).

Table 10: Within-treatment analyses for change from baseline to endpoint in mean sitting BP (mmHg) (ITT population) Study VEA A2302

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

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

The observed treatment differences in MSDBP between triple therapy and dual therapy that ranged between 3.3 and 5.3 mmHg are important since even a 2 mmHg reduction in diastolic blood

pressure results in a 6% reduction in the risk of coronary heart disease and a 15% reduction in the risk of stroke and transient ischemic attacks (Cook et al, 1995).[13]

The reduction in blood pressure with triple therapy was prompt with the full antihypertensive response being achieved 2 weeks after titration to the final and maximum dose. The beneficial effects of triple therapy on BP were not only demonstrated at trough (that is,, 23-26 hours after dosing) but also over the entire 24 hour dosing period and the daytime and night time hours compared to each of the dual therapies in the subset of patients with ABPM.

In moderate to severe hypertension, 71% of patients receiving triple therapy had their BP controlled (MSSBP/MSDBP <140/90 mmHg) compared to 45-54% for dual therapies (p<0.0001). Consistent results were observed for diastolic BP and systolic BP control rates and diastolic BP and systolic BP response rates.

The between-treatment comparison showed that triple therapy was clinically and statistically superior to all three dual therapies in reducing both diastolic and systolic BP at endpoint. Within and between treatment reductions in standing systolic and diastolic BP were similar to those observed for the sitting measurements.

Secondary efficacy results

Overall BP control was defined as MSSBP/MSDBP < 140/90 mmHg. At each assessment during the double blind period, significantly greater proportions of patients receiving triple therapy achieved overall BP control compared to those receiving any of the dual therapies.

At each assessment during the double blind period, significantly greater proportions of patients receiving triple therapy achieved overall BP control (Table 11), diastolic control (Table 12), systolic control (Table 13), diastolic response and systolic response compared to those receiving any of the dual therapies. Results at endpoint are shown in Table 14.

Table 11: Overall BP control rate at endpoint (ITT population) Study VEA A2302

Treatment comparison (A vs. B)	Treatment A n/N (%)	Treatment B n/N (%)	p-value
Val/HCTZ/Aml 320/25/10 vs. Val/HCTZ 320/25	404/571 (70.8)	267/553 (48.3)	<0.0001 *
Val/HCTZ/Aml 320/25/10 vs. Val/Aml 320/10	404/571 (70.8)	302/558 (54.1)	<0.0001 *
Val/HCTZ/Aml 320/25/10 vs. HCTZ/Aml 25/10	404/571 (70.8)	248/554 (44.8)	<0.0001 *

Overall BP control is defined as MSSBP/MSDBP < 140/90 mmHg
P-values were from a logistic model with treatment and region as factors.
* Indicates statistical significance at 0.05 level.

Table 12: Diastolic control rate at endpoint (ITT population) Study VEA A2302

Treatment comparison (A vs. B)	Treatment A n/N (%)	Treatment B n/N (%)	p-value
Val/HCTZ/Aml 320/25/10 vs. Val/HCTZ 320/25	463/571 (81.1)	362/553 (65.5)	<0.0001 *
Val/HCTZ/Aml 320/25/10 vs. Val/Aml 320/10	463/571 (81.1)	397/558 (71.1)	<0.0001 *
Val/HCTZ/Aml 320/25/10 vs. HCTZ/Aml 25/10	463/571 (81.1)	346/554 (62.5)	<0.0001 *

Diastolic control is defined as a MSDBP < 90 mmHg
P-values were from a logistic model with treatment and region as factors.
* Indicates statistical significance at 0.05 level.

[13] Cook N, Cohen J, Herbert P, et al. Implications of small reductions in diastolic blood pressure for primary prevention. Arch Intern Med 1995; 155: 701-709.

Table 13: Systolic control rate at endpoint (ITT population) Study VEA A2302

Treatment comparison (A vs. B)	Treatment A n/N (%)	Treatment B n/N (%)	p-value
Val/HCTZ/Aml 320/25/10 vs. Val/HCTZ 320/25	442/571 (77.4)	317/553 (57.3)	<0.0001 *
Val/HCTZ/Aml 320/25/10 vs. Val/Aml 320/10	442/571 (77.4)	340/558 (60.9)	<0.0001 *
Val/HCTZ/Aml 320/25/10 vs. HCTZ/Aml 25/10	442/571 (77.4)	308/554 (55.6)	<0.0001 *

Systolic control is defined as a MSSBP < 140 mmHg
P-values were from a logistic model with treatment and region as factors.
* Indicates statistical significance at 0.05 level.

Table 14: Control and response parameters at endpoint, Study VEA A2302 (ITT population)

	Val/HCTZ/Aml 320/25/10 mg n/N (%)	Val/HCTZ 320/25 mg n/N (%)	Val/Aml 320/10 mg n/N (%)	HCTZ/Aml 25/10 mg n/N (%)
Overall BP control	404/571 (70.8)*	267/553 (48.3)	302/558 (54.1)	248/554 (44.8)
Diastolic control	463/571 (81.1)*	362/553 (65.5)	397/558 (71.1)	346/554 (62.5)
Systolic control	442/571 (77.4)*	317/553 (57.3)	340/558 (60.9)	308/554 (55.6)
Diastolic responder	538/571 (94.2) [1]	460/553 (83.2)	505/558 (90.5)	479/554 (86.5)
Systolic responder	539/571 (94.4) [2]	474/553 (85.7)	497/558 (89.1)	477/554 (86.1)

Definitions: Overall BP control = MSSBP/MSDBP < 140/90 mmHg; diastolic control = MSDBP < 90 mmHg; systolic control = MSSBP < 140 mmHg; diastolic responder = MSDBP < 90 mmHg or ≥ 10 mmHg reduction from baseline; systolic responder = MSSBP < 140 mmHg or ≥ 15 mmHg reduction from baseline.
*Val/HCTZ/Aml statistically superior to dual therapy (p <0.0001)
[1] Val/HCTZ/Aml statistically superior to Val/Aml (p=0.0194); Val/HCTZ/Aml statistically superior to Val/HCTZ and HCTZ/AML (p <0.0001)
[2] Val/HCTZ/Aml statistically superior to Val/Aml (p=0.0014); Val/HCTZ/Aml statistically superior to Val/HCTZ and HCTZ/AML (p <0.0001)
P-values were from a logistic model with treatment and region as factors.

Ambulatory BP measurements: In total, 283 patients (67 – 76 per treatment group) participated in the ABPM portion of the study. All 4 treatments produced clinically relevant and statistically significant reductions in mean 24-hour ABP compared to baseline. Clinically and statistically significant greater reductions in both 24-hour systolic and diastolic ABP at endpoint were achieved with the triple combination (30.3/19.7 mmHg) compared to valsartan/HCT (23.9/15.5 mmHg), valsartan/amlodipine (24.1/14.9 mmHg), and HCT/amlodipine (18.8/11.7 mmHg). Consistent results were observed for both daytime and night time hours.

Open-label uncontrolled Study VEA ABR01

Study Design and Patient Characteristics

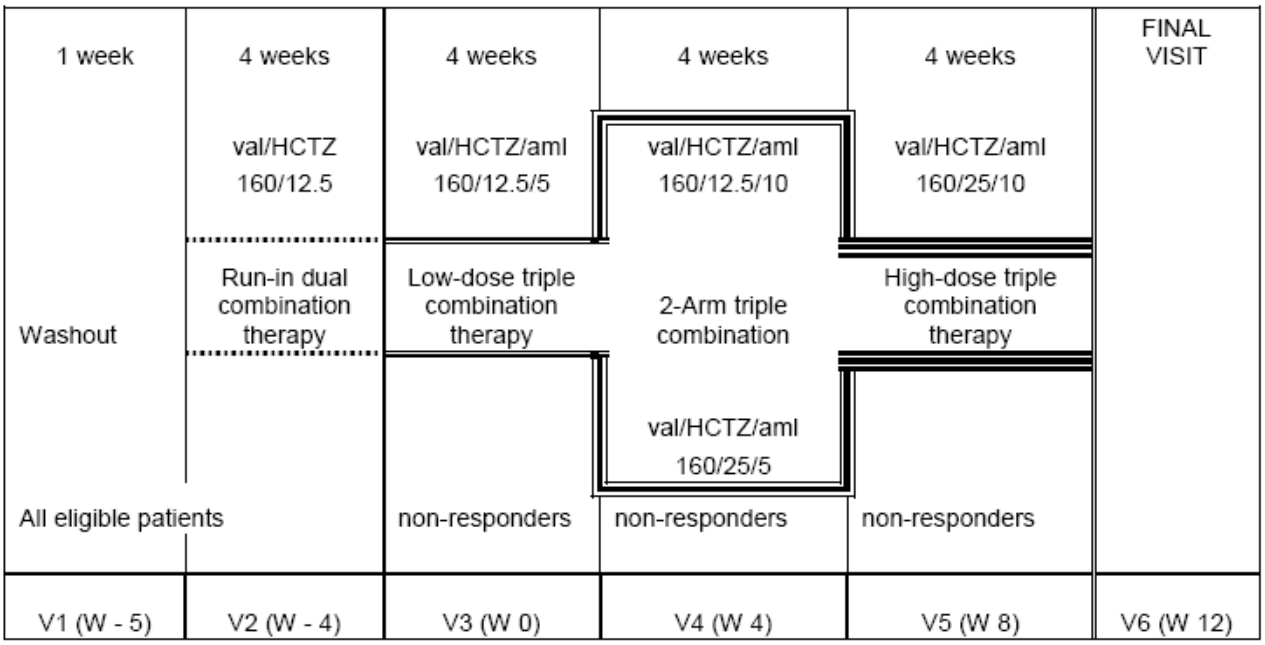
VEA ABR01 was a randomized, multicentre, two arm, parallel group study conducted at 15 centres in Brazil. Three hundred and forty patients were enrolled into the dual therapy run-in phase, and 326 (95.9%) completed this phase of the study. Two hundred and sixty four (264) patients entered the low-dose triple combination therapy phase (valsartan/HCT/amlodipine 160/12.5/5 mg); 182 of these patients subsequently entered the randomized 2-arm triple combination therapy phase and 82 patients were discontinued.

The objective of this study was to estimate the proportion of patients reaching blood pressure (BP) control after 12 weeks of treatment according to a valsartan/ HCT/amlodipine treatment algorithm in hypertensive patients not controlled with valsartan/HCT.

Eligible patients entered a run-in phase in which they received therapy with valsartan/HCT 160/12.5 mg for 4 weeks followed by an additional 4 weeks of treatment with valsartan/HCT/amlodipine 160/12.5/5 mg. At the end of this period, patients who did not meet target BP were randomized to

receive one of two higher dosage strengths of the triple therapy: either 160/12.5/10 mg or 160/25/5 mg (Figure 1).

Figure 1: VEA ABR01 Study design outline



Patients were categorized according to low, medium and high levels of cardiovascular risk. There were more randomized patients in the low risk group assigned to the valsartan/HCT/amlodipine 160/12.5/10 mg arm compared to the valsartan/HCT/amlodipine 160/25/5 mg arm. In the high risk group, more randomized patients were assigned to the valsartan/HCT/amlodipine 160/25/5 mg arm compared to the valsartan/HCT/amlodipine 160/12.5/10 mg arm.

After 4 weeks of randomized therapy, patients who still did not meet the target BP were allowed to increase the dose to 160/25/10 mg. Only patients who did not meet the target BP continued in the study at each titration-step. Patients who successfully met the target BP were withdrawn from the study. The duration of the study including all phases was 17 weeks.

The study population consisted of male and female hypertensive adult outpatients 18 years of age or older. Patients previously treated with a stable dose (as determined by the investigator) of up to 2 prior antihypertensive medications for a minimum of 2 months needed a MSSBP ≥ 140 mmHg and/or MSDBP ≥ 90 mmHg (OR a MSSBP ≥ 130 and/or a MSDBP ≥ 85 mmHg in subjects presenting with 2 or more risk factors OR a MSSBP ≥ 130 mmHg and/or a MSDBP ≥ 80 mmHg for those in the diabetic population) to enrol in the study. Previously untreated patients needed a MSSBP ≥ 160 mmHg and/or MSDBP ≥ 100 mmHg to enrol in the study.

Efficacy variables and statistical considerations

The primary efficacy variable was the proportion of patients who reached overall blood pressure control at endpoint (Week 12). Secondary efficacy variables were the proportion of patients who reached overall blood pressure control at Weeks 4, 8, and 12, diastolic and systolic blood pressure control rates at Weeks 4, 8, and 12, diastolic response rates, and mean change from study baseline in sitting and standing blood pressure after 4, 8 and 12 weeks of treatment.

Given the absence of firm data on which to base precise numerical assumptions about treatment efficacy, the sample size for the study was calculated on the premise that 40 patients with complete data would be needed to provide enough precision on the estimate of treatment efficacy at the end of 12 weeks. In other words, approximately 40 patients randomized to each of the two arms

would allow for the estimation of BP control rates with sufficiently narrow confidence intervals at endpoint. Assuming a BP control rate of 60% during the run-in phase (V2 to V3), subsequent response rates of 50% between V3 and V4, and V4 and V5, and a dropout rate of 15% during the study (V2 to V6), 460 patients were expected to be included in the run-in phase (V2). However, due to lower than expected BP control rates in the run-in phase, the trial stopped enrolment at 340 patients.

Patient Disposition and Baseline Characteristics

Demographic and baseline characteristics were generally comparable for the two triple therapy treatment strategies. The average age of all patients who received triple therapy was 56.5 years (ranging from 29 to 81 years). Patients in the valsartan/HCT/amlodipine 160/25/5 mg group were slightly older than those in the valsartan/HCT/amlodipine 160/12.5/10 mg group. Further, although the majority of patients in both randomized treatment strategies were younger than 65 years of age, there were slightly younger patients in the valsartan/HCT/amlodipine 160/12.5/10 mg group. Overall, and in both randomized treatment strategies, most of the patients were female, but this was more pronounced in the valsartan/HCT/amlodipine 160/12.5/10 mg group. At Week 0, the average MSSBP/MSDBP was 156/97 mmHg.

Most patients who received triple therapy had at least one past or continuing medical condition (82.2% overall), and these occurred at generally similar frequencies in the nonrandomized and randomized treatment strategies. The most frequently reported conditions (that is,, those reported for at least 20% of the patients overall) were metabolism and nutrition disorders (54.2%), musculoskeletal and connective tissue disorders (26.5%), surgical and medical procedures (22.7%), and eye disorders (20.8%)

Cardiovascular risk factors

Patients were categorized according to low, medium and high levels of cardiovascular risk. There were more randomized patients in the low risk group assigned to the valsartan/HCT/amlodipine 160/12.5/10 mg arm compared to the valsartan/HCT/amlodipine 160/25/5 mg arm. In the high risk group, more randomized patients were assigned to the valsartan/HCT/amlodipine 160/25/5 mg arm compared to the valsartan/HCT/amlodipine 160/12.5/10 mg arm.

The most frequently reported cardiovascular risk factors were related to family history and/or dyslipidaemia and/or patient age > 60 years. Patients with no cardiovascular risk factors comprised 15.2% of the total ITT population.

Efficacy results

For all ITT patients who received triple therapy, the proportion of patients who achieved blood pressure control at endpoint (Week 12) was 61.0%. The overall blood pressure control rates at Week 12 were similar for both randomized treatment strategies (43.9% for valsartan/HCT/amlodipine 160/12.5/10 mg; 45.8% for valsartan/HCT/amlodipine 160/25/5 mg) (Table 15).

Table 15: Blood pressure control rates by week and treatment strategy (ITT patients who received triple therapy) Study VEA ABR01

Week	Treatment	N'	BP controlled[1] n (%)	95% CI [2]
4	V160/H12.5/A5 (N=264)	264	60 (22.7)	(17.81, 28.26)
8	V160/H12.5/A10 (N=88)	87	21 (24.1)	(15.60, 34.50)
	V160/H25/A5 (N=94)	94	18 (19.1)	(11.76, 28.56)
12*	V160/H12.5/A10 (N=88)	66	29 (43.9)	(31.74, 56.70)
	V160/H25/A5 (N=94)	72	33 (45.8)	(34.02, 58.00)

N is the number of patients in ITT population; N' is the number of ITT patients with non-missing measurements at week 4, 8 and 12
[1] BP controlled was defined as follows: BP < 140/90 mmHg for low cardiovascular risk patients; BP < 130/85 mmHg for medium cardiovascular risk patients, and BP < 130/80 mmHg for high cardiovascular risk patients.
[2] Exact confidence intervals are presented.
*At week 12, patients in both randomized treatment arms received 160/25/10 mg

For all measurements of control and response, the greatest rates were achieved at Week 12.

Clinically relevant reductions in sitting blood pressure were achieved at all time points with all triple therapy regimens. At all time points, regardless of treatment group, the greatest blood pressure control rates were achieved in patients with low CV risk, followed by patients in the medium and high CV risk groups (Table 16).

In non-randomized triple therapy patients, sitting blood pressure was reduced by 16.3/9.3 mmHg after 4 weeks of treatment with valsartan/HCT/amlodipine 160/12.5/5 mg. At Week 8, which represents 4 additional weeks of randomized triple therapy, further reductions were achieved (14.8/8.5 mmHg for valsartan/HCT/amlodipine 160/12.5/10 mg; 13.5/8.4 mmHg for valsartan/HCT/amlodipine 160/25/5 mg). At Week 12, that is, after all patients had received 4 additional weeks of triple therapy with valsartan/HCT/amlodipine 160/25/10 mg, the reductions were similar regardless of prior randomized treatment assignment (20.4/11.5 mmHg for patients previously randomized to valsartan/HCT/amlodipine 160/12.5/10 mg; 22.2/12.6 mmHg for patients previously randomized to valsartan/HCT/amlodipine 160/25/5 mg). Results for standing blood pressure were similar to the sitting measurements.

Table 16: Blood pressure control rates by week, treatment strategy and cardiovascular risk category and (ITT patients who received triple therapy) Study VEA ABR01

Week	Treatment	CV risk	N'	BP controlled [1] n (%)	95% CI [2]
4	V160/H12.5/A5 (N=264)	Low	96	33 (34.4)	(24.98, 44.77)
		Medium	83	19 (22.9)	(14.38, 33.42)
		High	85	8 (9.4)	(4.15, 17.71)
8	V160/H12.5/A10 (N=88)	Low	31	10 (32.3)	(16.68, 51.37)
		Medium	26	8 (30.8)	(14.33, 51.79)
		High	30	3 (10.0)	(2.11, 26.53)
	V160/H25/A5 (N=94)	Low	22	7 (31.8)	(13.86, 54.87)
		Medium	31	6 (19.4)	(7.45, 37.47)
		High	41	5 (12.2)	(4.08, 26.20)
12*	V160/H12.5/A10 (N=88)	Low	20	11 (55.0)	(31.53, 76.94)
		Medium	19	10 (52.6)	(28.86, 75.55)
		High	27	8 (29.6)	(13.75, 50.18)
	V160/H25/A5(N=94)	Low	14	9 (64.3)	(35.14, 87.24)
		Medium	21	10 (47.6)	(25.71, 70.22)
		High	37	14 (37.8)	(22.46, 55.24)

N is the number of patients in ITT population; N' is the number of ITT patients with non-missing measurements at week 4, 8 and 12
[1]Definitions of BP control:
MSSBP <140 mmHg and MSDBP <90 mmHg for low risk patients;
MSSBP <130 and MSDBP <85 mmHg for medium risk patients;
MSSBP <130 and MSDBP <80 mmHg for high risk patients.
[2] Exact confidence intervals are presented.
*At week 12, patients in both randomized treatment arms received 160/25/10 mg

Comments: Open-label uncontrolled study VEA ABR01 is the only triple combination add-on study submitted in this submission. This study evaluated the add-on effect of an extra 5mg of amlodipine or an extra 12.5mg of HCT for those patients who did not respond to a regimen of amlodipine/valsartan/ HCT 5/160/12.5mg. However, it appears that there could have been patients who were only on this add-on therapy for a further 4 weeks before the final assessment. Another important deficiency of this study would appear to be that only patients who did not meet the target BP continued in the study at each titration step. Patients who successfully met the target BP were withdrawn from the study. This means that for these latter patients there are no data available on maintenance of effect.

Long-term open-label Study VAA A2201E1

Study Design and Patient Characteristics

VAA A2201E1 was a 52-week, multicentre, open-label extension study to Protocol 2201 in 1300 patients with mild to moderate uncomplicated essential diastolic hypertension (grades 1 and 2 WHO classification). The study was conducted in 139 centres in 6 countries (Belgium, Canada, France, Germany, Mexico, and the US).

The primary objective of this 52-week open label extension was to further evaluate the safety, tolerability and long-term efficacy of once daily administration of the combination of valsartan/amlodipine 80/2.5, 80/5, 160/5, or 160/10 mg, alone or in combination with HCT (HCT) 12.5 mg. The study was completed as planned.

Up to 1300 patients from all participating centres around the world who successfully completed the double-blind phase were allowed to enter the open-label extension. After successfully completing 8 weeks of double-blind treatment in Protocol VAA A2201 without serious drug related adverse experiences, patients with a MSDBP <90 mmHg and a MSSBP <140 mmHg wishing to continue treatment with valsartan/amlodipine were eligible to enter this 52-week open-label extension.

Patients were enrolled directly from the double-blind phase into the open-label extension, without a washout period and with no prior knowledge of treatment they received in the core protocol.

The inclusion and exclusion criteria were the same as in the core trial. Patients who successfully completed 8 weeks of double-blind treatment in Study 2201 were eligible to enter the extension. Two additional criteria were:

The patient's blood pressure at Visit 7 (week 8) of the Protocol 2201 trial had to be well controlled (defined as MSDBP <90 mmHg, and MSSBP <140mmHg). At the investigator's discretion, patients with MSDBP >90 mmHg but $\leq$ 95 mmHg, and MSSBP >140 but $\leq$ 150 mmHg could participate in the extension if this was considered an acceptable level of blood pressure control for the patient.

Patients who experienced any adverse events considered serious and drug related in Study 2201] were excluded.

Patients were randomized in an open-label fashion to receive either valsartan/amlodipine 80/2.5 mg od (low dose group) or 80/5 mg od (high dose group) for a period of four weeks.

Subsequently, patients without symptomatic hypotension or significant peripheral oedema were force titrated to valsartan/amlodipine 160/5 mg od (low dose group) or 160/10 mg od (high dose group), respectively, for the remainder of the trial. Patients whose MSDBP remained $\geq$ 90 mmHg or whose $\geq$ 140 mmHg with no clinical signs of hypovolaemia, at any dose MSSBP remained following the initial titration period, could have added HCT 12.5 mg. Patients who experienced intolerable adverse experiences at any point following up-titration to the higher doses (that is, valsartan/amlodipine 160/5 or 160/10 mg) could be back titrated to a prior dose combination of valsartan/amlodipine, with or without HCT.

Efficacy variables and statistical consideration

The primary efficacy variable was the change from baseline in mean sitting diastolic blood pressure (MSDBP) at trough. The secondary efficacy variable was change from baseline in mean sitting systolic blood pressure (MSSBP) at trough. Other efficacy variables were change from baseline in standing diastolic and systolic blood pressures, and sitting and standing pulse.

Statistical methods: The randomization visit (Visit 2) of the core study was defined as the baseline for all analyses. Data gathered in the extension trial were summarized with respect to the following:

1. Background and demographic characteristics.
2. Safety observations and measurements.
3. Efficacy observations and measurements.

The core-baseline was used as the baseline for the extension study. The endpoint for the extension study was derived by using the method of the last-observation-carried-forward (LOCF), that is, the last non-missing post randomization visit of the extension study (visit 8) evaluation.

The sample size was chosen based on ICH requirements for long term exposure. Sample size was not based on any efficacy criteria or power considerations. Up to 1300 patients from all participating centres around the world who successfully completed the double-blind phase were allowed to enter the open-label extension.

The vast majority of extension patients were Caucasian (83.0%) and younger than 65 years of age (83.1%), with a mean age of 54.2 overall. There was a very slight majority of male patients.

Patient Disposition and Baseline Characteristics

A total of 1246 patients participated in this open-label extension study; 1075 (86.3%) completed the trial. At least 150 and up to 156 patients in the low-dose group and at least 97 and up to 115 in the high-dose group were known to have had HCT added to their treatment regimen during the extension trial; thus, at least 247 and up to 271 patients in the study received triple therapy. (A small proportion of patients took incorrect doses of study medication, or took no treatment at all for a specific period of time. In general, treatment violations were temporary, and most patients resumed their correct treatment/doses soon after the violation occurred.) The maximum duration of exposure to triple therapy in this study as per protocol was 44 weeks.

The treatment groups were balanced with regard to blood pressure and pulse values obtained at baseline of the core study. Patients who required the addition of HCT had higher baseline sitting and standing blood pressures than those who remained on valsartan/amlodipine alone.

Efficacy Results

For MSDBP and MSSBP at trough, similar blood pressure lowering effects were seen in both the low and high dose groups (Table 17). Reductions in blood pressure at endpoint in the subgroup of patients who added HCT was not greater than in patients who remained on dual therapy. This is likely due to the fact that this was a selected population whose blood pressure may have been more difficult to control since only patients uncontrolled on dual therapy were given the opportunity to add HCT to their regimen.

Table 17: Changes from core-baseline in MSDBP and MSSBP (mmHg) at trough by randomized treatment group, Study VAA A2201E1 (all extension patients)

	High Dose					
Variable	**Val/Aml**		**Val/Aml/HCTZ**		**Total**	
	N*	**Mean (SD)**	**N***	**Mean (SD)**	**N***	**Mean (SD)**
MSDBP endpoint**	506	-18.2 (7.4)	115	-17.7 (8.1)	621	-18.1 (7.5)
MSSBP endpoint**	506	-23.1 (14.5)	115	-21.6 (13.8)	621	-22.8 (14.3)
	Low dose					
Variable	**Val/Aml**		**Val/Aml/HCTZ**		**Total**	
	N*	**Mean (SD)**	**N***	**Mean (SD)**	**N***	**Mean (SD)**
MSDBP endpoint**	462	-17.8 (7.7)	154	-15.3 (7.4)	616	-17.2 (7.7)
MSSBP endpoint**	462	-21.5 (14.1)	154	-23.8 (13.7)	616	-22.1 (14.0)

(*)N is the number of patients with values obtained at both core-baseline and extension visit.
(**)Endpoint is Week 52, or last visit carried forward.

Comment: The original VAA A2201E1 study protocol and the final study report were not available in the submission. The open-label extension of study VAA A2201E1 is the only long term study (conducted over 52 weeks) in the submission. The efficacy results of this study showed that the reduction in mean MSDBP and MSSBP for the high dose triple combination was less than corresponding reductions for the high dose dual combination of valsartan/amlodipine. For the low dose combinations, the reduction of mean MSDBP was again less on triple therapy as compared with the dual combination. For the low dose combinations, only the reduction in mean MSSBP was greater on triple therapy as compared with the dual combinations. This is likely due to the fact that this was a selected population of patients whose blood pressure may have been more difficult to control. However, in an add-on study, this is the selected group of patients for whom the third drug would be added to demonstrate the efficacy of the triple combination. Furthermore, there are no data which examined the response in non-responders, that is, the percentage of non-responders

whose blood pressure came under satisfactory control with the addition of the third agent, in this case HCT. Based on the above results, it would appear that the extension of study VAA A2201E1 has not provided any data which suggest a significant add-on effect of HCT when added to dual therapy.

Other completed studies

Exposure to the triple combination occurred through the double-blind or optional, open-label addition during the late phase of the study either of HCT to valsartan/amlodipine (studies [VAA A2401], [VAA A2402], [VAA A2403]), or of amlodipine to valsartan/HCT (studies [VAH BUS04], [VAH BDE13E1], [VAH B2406E1]), or of valsartan to amlodipine/HCT (Study [VAH B2406E1]). Efficacy data from each of these six clinical studies are reported individually in the respective Clinical Study Reports, according to the study objectives for the randomized regimens in the study. These studies are briefly summarized below for completeness, and are not discussed further. Efficacy was not evaluated in the subgroup of patients who received triple therapy in these trials.

Study VAA A2401

This was a double-blind, randomized, multicentre study conducted at 118 centres in 8 countries (Belgium, Canada, France, Norway, Slovakia, Spain, Switzerland, and the US). Eligible patients were randomized in a 1:1 ratio to receive either valsartan/amlodipine 160/5 mg or valsartan/amlodipine 160/10 mg. At Week 8, HCT 12.5 mg open label was added if the patient was uncontrolled, that is, mean blood pressure (MBP) ≥ 140/90 mmHg for non-diabetics or ≥ 130/80 mmHg for diabetics. HCT was not added if the blood pressure was controlled.

At Week 12, if the patient remained uncontrolled, an additional 12.5 mg HCT open label was added to the treatment (total daily dose of 25 mg or 12.5 mg for patients with controlled BP at Week 8). HCT was not uptitrated if the patient was controlled. The duration of the study, including all phases, was 17-18 weeks.

The primary efficacy variable was the proportion of patients who achieved blood pressure control at endpoint (Week 16), defined as BP <140/90 mmHg for non-diabetic patients or BP <130/80 mmHg for diabetic patients. Secondary efficacy variables were the proportion of patients who reached blood pressure control at pre-HCT endpoint (Week 8), the number of BP controlled patients by study week, change from baseline in MSDBP and MSSBP, and diastolic BP control rate. As previously noted, efficacy was not evaluated in the subgroup of patients who received triple therapy in this trial.

Study VAA A2402

This was a 12-week double-blind, randomized, multicentre, parallel group study conducted at 74 centres in 4 countries (Colombia, Ecuador, South Africa, and the US) in Black patients with stage II hypertension. Eligible patients were randomised in a 1:1 ratio to receive valsartan/amlodipine 160/5 mg or valsartan/amlodipine 160/10 mg for 2 weeks, followed by the forced-titration schedule.

At Week 8, patients in either treatment regimen who had not reached target for systolic blood pressure (MSSBP <130 mmHg) could have HCT 12.5 mg open label medication added at the discretion of the investigator.

The primary efficacy variable was change from baseline in MSSBP (mmHg) at Week 8 LOCF. Secondary efficacy variables were:

- Change from baseline MSDBP at Week 8 LOCF.
- Change from baseline MSSBP and MSDBP at Weeks 2, 4 and 8 and 12.

• Overall BP control rate after 12 weeks of treatment (MSSBP <140 mmHg and MSDBP <90 mmHg).

As previously noted, efficacy was not evaluated in the subgroup of patients who received triple therapy in this trial.

Study VAA A2403

This was an 8-week double-blind, randomized, multicentre, parallel group study conducted in 75 centres in 6 countries (Belgium, Denmark, Italy, Poland, Spain and US). Eligible patients were randomized in a 1:1 ratio to receive valsartan/amlodipine 160/5 mg or amlodipine 5 mg for 2 weeks, followed by a forced-titration schedule. At Week 4, patients in either treatment regimen who had not reached target for mean systolic blood pressure (MSSBP <130 mmHg) could add 12.5 mg HCT open-label medication at the discretion of the investigator.

The primary efficacy variable was change from baseline in MSSBP (mmHg) at Week 4 (LOCF). Secondary efficacy variables were:

• Change from baseline MSDBP at pre-HCT Week 4 (LOCF)

• Change from baseline MSSBP and MSDBP at Weeks 2, 4, and 8

• Overall BP control rate after 8 weeks of treatment (MSSBP <140 mmHg and MSDBP <90 mmHg)

A total of 646 patients were randomized and 577 (89.3%) completed the study, 289 (89.8%) in the valsartan/amlodipine group and 288 (88.9%) in the amlodipine group. A total of 136 patients in the valsartan/amlodipine treatment strategy received triple therapy through the addition of HCT 12.5 mg. Patients who received valsartan/amlodipine 160/10 mg exhibited significantly greater reductions from baseline in MSSBP at Week 4 than did those who received amlodipine 10mg. At week 8, some patients in the valsartan/amlodipine group could have been receiving the triple combination of valsartan/HCT/amlodipine and some patients in the amlodipine group could have been receiving amlodipine/HCT starting at Week 4. At week 8, the mean changes from baseline in both MSSBP and MSDBP were greater in the valsartan/amlodipine group [- 32.0 mmHg (p=<0.0001) and -13.9 mmHg (p= <0.0001), respectively)] compared to the amlodipine group (-26.4 mmHg and -9.4 mmHg).

Study VAH BUS04

This was a multicentre, randomized, double-blind, double-dummy, active controlled, parallel-group trial conducted at 50 study centres in the United States. The study was designed to evaluate the effects of valsartan/HCT 160/12.5 mg in comparison with HCT 25 mg monotherapy in patients whose BP was uncontrolled by HCT 12.5 mg monotherapy. Eligible patients were assigned to 4 weeks of single-blind treatment with HCT 12.5 mg.

After 4 weeks of treatment with HCT 12.5 mg, eligible patients who did not achieve BP control (mean seated SBP value < 140 mmHg and mean seated DBP value < 90mmHg) were randomized to 4 weeks of double-blind treatment with valsartan/HCT 160/12.5 mg or HCT 25 mg. Following the 4-week core double-blind treatment period, eligible patients were assigned to a maximum 16 weeks of open-label treatment. Patients not demonstrating BP control at Week 8 were titrated upward to valsartan/HCT 320/25 mg.

Patients not demonstrating BP control at Week 12 were titrated upward to valsartan / HCT / amlodipine 320/25/5 mg. Patients not demonstrating BP control at Week 16 were titrated upward to valsartan/HCT/amlodipine 320/25/10 mg for the remaining 28 days of the trial. Only patients with uncontrolled BP continued in the study at each titration-step. Once a patient's BP was controlled, they were withdrawn from the study.

The primary efficacy variable was the percentage of patients attaining BP control (defined as MSSBP of < 140 mmHg and MSDBP < 90 mmHg); the primary time point was Week 4. Week 2 and Week 20 were secondary time points. The secondary efficacy variables were:

- Change in MSSBP from baseline to Week 2 and Week 4.
- Change in MSDBP from baseline to Week 2 and Week 4.
- Change in MSSBP from Week 4 to Week 20.
- Change in MSDBP from Week 4 to Week 20.

As previously noted, efficacy was not evaluated in the subgroup of patients who received triple therapy in this trial.

Study VAH BDE13E1

This was a multicentre, open-label, two-stage study conducted at 40 sites in Germany. The study was designed to evaluate the efficacy and safety of valsartan /HCT 160/25 mg od in fixed dose combination (FDC) for 4 weeks in patients with essential hypertension not adequately controlled by 4 weeks of therapy with candesartan/HCT 32/25 mg od in free combination. Eligible patients received one week of treatment with candesartan/HCT 16/12.5 mg od in free combination, followed by three weeks of treatment with candesartan /HCT 32/25 mg od in free combination. Patients with inadequate blood pressure control (defined as a MSDBP at trough of ≥ 90 mmHg) at the end of the first treatment phase (Week 4) received treatment with valsartan/HCT 160/25 mg od in FDC for an additional 4 weeks. Patients still uncontrolled at Week 8 entered the open-label, single-arm extension phase and were treated with amlodipine 5 mg in addition to valsartan/HCT 160/25 mg FDC for an additional 4 weeks.

The primary efficacy parameter of the core phase of this trial was the change in trough MSDBP between Week 4 (candesartan/HCT 32/25 mg in free combination) and Week 8 (valsartan/HCT 160/25 mg in FDC). The primary efficacy parameter of the extension was the change in trough MSDBP between Week 8 and Week 12. The secondary efficacy parameters were:

- changes in trough MSSBP
- changes in pulse pressure
- changes in pulse rate
- responder rates (systolic responder rate at Week 12 defined as a MSSBP < 140 mmHg or 20 mmHg decrease compared to Week 8 and diastolic responder rate at Week 12 defined as a MSDBP < 10 mmHg decrease compared to Week 8).90 mmHg or ≥ ≥
- normalization rate (defined as MSSBP < 140 mmHg and/or MSDBP < 90 mmHg)

As previously noted, efficacy was not evaluated in the subgroup of patients who received triple therapy in this study.

Study VAH B2406E1

This was a randomized, double-blind, parallel group, active-controlled, multi-centre, 14 week study and 8 week extension to evaluate the effectiveness of a valsartan versus an amlodipine treatment strategy in achieving blood pressure control in patients with stage 1 or stage 2 hypertension or uncontrolled on present monotherapy. The study was conducted at 122 centres in 11 countries including Argentina, Brazil, Colombia, Germany, Denmark, Ecuador, Spain, Finland, United Kingdom, Ireland and Italy.

In the core study, eligible patients were randomized in a 1:1 ratio to a valsartan treatment strategy or an amlodipine treatment strategy. Patients could be up titrated or down titrated to reach BP control

(MSSBP < 140 mmHg and MSDBP < 90 mmHg) by increasing or decreasing the dose of valsartan or amlodipine, or adding, increasing, or decreasing HCT.

The extension study was an 8-week double-blind, parallel group, active-controlled, multicentre extension study with two treatment arms. Patients completing the 14-week core study with uncontrolled BP (MSSBP ≥ 140 mmHg and/or MSDBP ≥ 90 mmHg) could be enrolled in this extension study and receive triple therapy by the addition of either amlodipine 5 mg or valsartan 160 mg, depending on their treatment in the core study. At Week 18, if patients were still not at BP control, amlodipine and valsartan were up titrated to 10 mg and 320 mg respectively.

The primary efficacy variable in the core study was the percentage of patients attaining BP control (defined as MSSBP of < 140 mmHg and MSDBP < 90 mmHg) at the end of the core study (Week 14). The secondary efficacy variables in the core study were blood pressure control at Weeks 4, 8, and 11, time to blood pressure control, and MSDBP and MSSBP at Weeks 4, 8, 11, and 14. The primary efficacy variable in the extension study was the percentage of patients who reached BP control at the end of the extension study (Week 22).

As previously noted, efficacy was not evaluated in the subgroup of patients who received triple therapy in this trial.

Comment : Studies [VAA A2401], [VAA A2402], [VAAA2403], [VAH BUS04], [VAH BDE13E1] and [VAH B2406E1] have been included as supportive studies for the submission. Nevertheless, in these studies the subgroup of patients who received triple therapy was not separately evaluated. Hence, these studies do not contribute efficacy data to this application and the only relevant information was regarding safety.

Summary of Efficacy

The pivotal Study VEA A2302 is of adequate design and addressed the indications being sought for Exforge HCT in the sponsor's application. The primary efficacy results showed that clinically relevant and statistically significant reductions from baseline in MSDBP and MSSBP were achieved at endpoint with all 4 treatments. The greatest reductions were observed with triple therapy. The between-treatment comparisons showed that triple therapy was clinically and statistically superior to all three dual therapies in reducing both diastolic and systolic BP at endpoint in the ITT population and in the Per Protocol population.

Secondary efficacy results in pivotal Study VEA A2302 demonstrated that significantly greater proportions of patients receiving triple therapy achieved overall BP control compared to those receiving any of the dual therapies.

In the Open-label uncontrolled Study VEA ABR01, of all patients who received triple therapy (including patients in the single-arm treatment phases), the proportion of patients who achieved blood pressure control at endpoint (Week 12 or LOCF) was 61.0%**.** At all time-points assessed, regardless of treatment group, the greatest blood pressure control rates were achieved in patients with low CV risk followed by the medium and high CV risk groups.

In the long-term Study VAA A2201E1 after 4 weeks of treatment in the open label extension, the high-dose patients and the low-dose patients had reductions from core baseline in MSDBP at Week 4. After being force-titrated, greater reductions in MSDBP at Week 8 were observed. Further reductions were observed over time starting at Week 13 with the optional addition of HCT which could occur as early as Week 8. Reductions at endpoint were 18.1 mmHg for high dose and 17.2 mmHg for low dose valsartan/amlodipine.

In studies [VAA A2401], [VAA A2402], [VAA A2403], [VAH BUS04], [VAH BDE13E1], and [VAH B2406E1] efficacy was not evaluated in the subgroup of patients who received triple therapy.

Safety

Overview of clinical trials which contributed safety data

The safety assessments consisted of the regular monitoring and recording all adverse events (AE) and serious adverse events (SAE), physical examination, pulse rate, weight, laboratory evaluations (haematology and blood chemistry), and pregnancy testing.

The total number of patients exposed to triple therapy in the safety population was at least 1789 and up to 1813. The trials or sources of data which contributed to the assessment of safety comprised:

Clinical studies with the objective of assessing the valsartan/HCT/amlodipine triple combination - these were referred to as the VEA studies. These included the large phase III double-blind study A2302, involving 2268 patients (559-582 per treatment arm) and the open-label phase III supportive study VEA ABR01 involving 340 patients (264 patients in the safety population received triple therapy).

There was one long-term, open-label extension trial designed to evaluate valsartan/amlodipine with the optional addition of open-label HCT study VAA A2201E1, where some patients could have been counted in more than one dose group, at least 247 and up to 271 patients were known to have received triple combination therapy.

Clinical studies with triple combination exposure by adding HCT to valsartan/amlodipine during the late phase of the study were labelled as the VAA studies. Three short-term, double-blind studies (VAA A2401, VAA A2402 and VAA A2403) designed to evaluate valsartan/amlodipine with the optional addition of open-label HCT.

Clinical studies with triple combination exposure by adding amlodipine to valsartan/HCT OR valsartan to HCT/amlodipine during the late phase of the study were referred to as the VAH studies. Two trials with optional open-label addition of amlodipine to valsartan/HCT (VAH BUS04 and VAH BDE13E1) and one trial with double-blind addition of amlodipine to valsartan/HCT or valsartan to HCT/amlodipine. .

The number of patients in the safety population who received triple combination therapy in the 6 completed supportive studies were; 196 in study VAA A2401, 147 in Study VAA A2402, 136 in Study VAA A2403, 72 in Study VAH BUS04, 66 in Study VAH BDE13E1, and 79 in Study VAH B2406E1.

Summary of inclusion and exclusion criteria

Patient selection criteria were chosen based on the known safety profiles of angiotensin receptor blockers, HCT and calcium channel blockers, and the need to avoid confounding factors that could influence the primary efficacy variable. The key efficacy and safety trials randomized male and female adult patients with hypertension according to the study-specific definitions.

Safety in Pivotal Study VEA A2302

Patient Characteristics and Drug Exposure

The treatment groups were generally comparable with respect to the demographic characteristics. Caucasians comprised 71.6% of the randomized population, and 55.3% were male. The mean age was 53.2 years, with 14.0% being 65 years of age and older and 1.8% being 75 years of age and older.

In Study VEA A2302, exposure to study drug was similar across all treatment groups, and consistent with the 8-week double-blind treatment duration.

Adverse Events

In the total safety population, 45.9% of the patients (45% to 48% across treatment groups) had at least one adverse event during the double-blind treatment period. Most events were mild to moderate in severity, and not suspected to be study drug related. The most frequently reported AEs in the total safety population were peripheral oedema (5.7%), headache (5.4%), and dizziness (5.2%). The frequencies of AEs were similar across treatment groups with the exception of dizziness and peripheral oedema. Dizziness occurred more often with triple therapy (7.7%) and valsartan/HCT (7.0%) than with valsartan/amlodipine (2.3%) or HCT/amlodipine (3.9%). The incidence of peripheral oedema with the triple therapy (4.5%) was less than that reported with valsartan/amlodipine (8.5%) and HCT/amlodipine (8.9%) but greater that that reported with valsartan/HCT (0.9%). Otherwise, all treatment groups were generally comparable with regard to rates and severity of AEs. Triple combination therapy was well-tolerated regardless of age, gender, and race. The number (percent) of patients with suspected study drug-related adverse events by preferred term (greater than or equal to 2 percent for any treatment group) is shown in Table 18.

Table 18: Number (percent) of patients with suspected study drug-related adverse events by preferred term (greater than or equal to 2 percent for any treatment group) (Safety population)

Study VEA A2302

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

* Preferred terms are sorted by total incidences (descending) in the Val/HCTZ/Aml treatment group.

Deaths, Serious AEs and discontinuation due to AEs

No deaths occurred during the study. Serious adverse events were rare (21 patients; 0.9% in the total safety population; 0.7% to 1.3% across treatment groups), occurred at similar frequencies across treatment groups, were not usually suspected to be study drug related, and were not clustered in any particular system organ class. Not more than one patient in any treatment group experienced any individual SAE.

A total of 67 patients (3% of the total safety population; 1.6% to 4.0% across treatment groups) were discontinued from the study due to AEs that had an onset during the double-blind phase. Discontinuations due to AEs occurred slightly less often in the valsartan/amlodipine treatment group (1.8%) than in the other three treatment groups (3.0% – 4.1%). The most frequently reported AEs leading to discontinuation were dizziness (15 patients, 0.7%), hypotension (10 patients, 0.4%) and peripheral oedema (8 patients, 0.4%).

Laboratory changes

Laboratory changes with the triple combination were consistent with known effects of HCT and valsartan. The presence of valsartan in both the triple combination therapy group and the dual combination group with HCT attenuated the hypokalaemic effect of HCT.

Orthostatic blood pressure changes (defined as a decrease of at least 20 mm Hg in systolic blood pressure or a decrease of at least 10 mm Hg in diastolic blood pressure when a patient moves from a sitting position to a standing position) were exhibited by 10.1% of the total safety population (9.7%

to 10.7% across treatment groups) at one or more post-baseline visit. Orthostatic hypotension was reported as an AE in 4 patients (one on triple therapy; two on valsartan/HCT and one on HCT/amlodipine). Two patients in the valsartan/HCT group were discontinued due to orthostatic hypotension reported as an AE, one of which was serious. Only small changes from baseline in sitting and standing pulse rate and weight were observed at endpoint.

Safety in Study VEA ABR01

Patient Characteristics and Drug Exposure

Demographic and baseline characteristics were generally comparable for the two triple therapy treatment strategies. The average age of all patients who received triple therapy was 56.5 years (ranging from 29 to 81 years). Patients in the valsartan/HCT/amlodipine 160/25/5 mg group were slightly older than those in the valsartan/HCT/amlodipine 160/12.5/10 mg group. Further, although the majority of patients in both randomized treatment strategies were younger than 65 years of age, there were slightly younger patients in the valsartan/HCT/amlodipine 160/12.5/10 mg group. Overall, and in both randomized treatment strategies, most of the patients were female, but this was slightly more pronounced in the valsartan/HCT/amlodipine 160/12.5/10 mg group.

Adverse Events

The adverse events seen in the study were as expected for this population and the classes of drug that made up the combination therapies. They were mostly mild and transient, did not appear to be dose-related (except for peripheral oedema) and gave no indication of target organ toxicity. During Week -4 to 0 (dual therapy), AEs occurred in 18.5% of the patients. The most frequently reported AE during this phase of the study was headache (3.2%).

During Week 0 to 4 (non-randomized low dose triple therapy), AEs occurred in 52.4% of the patients. The most frequently reported AEs during this phase were peripheral oedema (8.5%), impaired glucose tolerance (6.1%) and headache (4.9%).

During Weeks 0 to 12, AEs occurred in 64.8% of the patients randomized to valsartan / HCT / amlodipine 160/12.5/10 mg, and 60.6% of the patients randomized to valsartan/HCT/amlodipine 160/25/5 mg (Table 19). The most frequently reported AEs in both groups were peripheral oedema, headache and dizziness. Peripheral oedema occurred more often in patients randomized to valsartan/HCT/amlodipine 160/12.5/10 mg (35.2%) than in patients randomized to valsartan/HCT/amlodipine 160/25/5 mg (21.3%). Headache and dizziness occurred at similar frequencies in both treatment groups. It was also noted that back pain occurred more often with valsartan/HCT/amlodipine 160/12.5/10 mg (6.8%) than with valsartan/HCT/amlodipine 160/25/5 mg (1.1%). Arthralgia occurred in 4.3% valsartan/HCT/amlodipine 160/25/5 mg group versus none in the valsartan/HCT/amlodipine 160/12.5/10 mg group. Otherwise, AEs occurred at comparable frequencies in the two randomized treatment groups. The pattern of AE reporting during the study as described above shows a greater overall incidence of AEs being reported during the valsartan/HCT/amlodipine triple therapy treatment phases compared to the valsartan/HCT dual therapy phase. This was due in part to the increased incidence of peripheral oedema in the triple therapy phase as expected with the addition of amlodipine to the dual therapy of valsartan/HCT.

AEs related to laboratory and metabolic abnormalities were also reported more frequently in the triple therapy phases compared to dual therapy. This observation was unexpected based on the known safety profile of amlodipine and is likely due to the fact that the first laboratory tests after initiating study drug were not performed during the initial dual therapy phase but only after the patient had completed 4 weeks of triple therapy. Thus, laboratory and metabolic AEs that may have developed during the dual therapy phase (likely due to the HCT component) were actually captured during the triple therapy phase. A time effect may also have contributed to the AE profile observed in this study as patients were receiving triple therapy for a longer period of time compared to dual therapy.

Table 18: Adverse events (greater than or equal to 2 percent in any triple therapy group) suspected to be study drug related (Safety population, Study VEA ABR01)

	Dual therapy	Triple Therapy		
	(Wk -4 to 0)	Non-randomized (Wk 0 to 4)	Randomized treatment (Wk 0 to 12)	
Preferred term	Val/HCTZ 160/12.5 mg N=340 n (%)	Val/HCTZ/Aml 160/12.5/5 mg N=82 n (%)	Val/HCTZ/Aml 160/12.5/10 N=88 n (%)	Val/HCTZ/Aml 160/25/5 N=94 n (%)
All "suspected" preferred terms	8 (2.4)	21 (25.6)	35 (39.8)	24 (25.5)
Peripheral edema	2 (0.6)	7 (8.5)	31 (35.2)	15 (16.0)
Edema NOS	0 (0.0)	1 (1.2)	1 (1.1)	2 (2.1)
Impaired glucose tolerance	0 (0.0)	4 (4.9)	0 (0.0)	1 (1.1)
Headache	0 (0.0)	3 (3.7)	0 (0.0)	1 (1.1)
Pain in extremity	0 (0.0)	0 (0.0)	1 (1.1)	2 (2.1)
Dizziness	3 (0.9)	0 (0.0)	2 (2.3)	0 (0.0)
Nausea	1 (0.3)	2 (2.4)	0 (0.0)	0 (0.0)

AEs possibly associated with low blood pressure either did not occur, or occurred at very low frequencies. Hypotension occurred in one patient in the low dose triple therapy group (1.2%). Most events were mild to moderate in severity, and not suspected to be study drug related.

Deaths, Serious AEs and Discontinuations due to AEs

No deaths occurred during the study. Serious adverse events were rare, occurring in only 2 patients in the total safety population. In both instances, the SAEs were not suspected to be study drug related, did not lead to discontinuation and were not clustered in any particular system organ class. A total of 18 patients (5.3%) were discontinued from the study due to AEs. Three patients (0.9%) were discontinued due to AEs during the dual therapy period (Week -4 to 0): One patient was discontinued due to dizziness, one was discontinued due to abdominal pain and diarrhoea, and one was discontinued due to migraine. Of these events, only the dizziness was suspected to be study drug related. Ten non-randomized patients (12.2%) on low-dose triple therapy were discontinued due to AEs with an onset during Weeks 0 to 4. Peripheral oedema led to the discontinuation of 3 patients (3.7%); 2 patients (2.4%) were discontinued due to nausea. All other preferred terms occurred in ≤ 1 patient. Most of these AEs were suspected to be study drug related. Five randomized patients were discontinued due to AEs with an onset after Week 4 (2 patients, 2.3% in the valsartan/HCT/amlodipine 160/12.5/10 mg group, and 3 patients, 3.2%, in the valsartan/HCT/amlodipine 160/25/5 mg group). In the valsartan/HCT/amlodipine 160/12.5/5 mg group, one patient was discontinued due to peripheral oedema, and another was discontinued due to somnolence. Both events were suspected to be study drug related. In the valsartan/HCT/amlodipine 160/25/5 mg group, two patients were discontinued due to peripheral oedema (one also had a rash), and another was discontinued due to malaise, increased sweating and tachycardia. Neither case of peripheral oedema was suspected to be study drug related; all other AEs reported by these patients were suspected to be study drug related.

Vital Signs and Laboratory Changes

For all haematology parameters and biochemistry parameters, no significant differences in laboratory profiles were observed with the combinations of valsartan/HCT/amlodipine. Only small changes in pulse were observed. Orthostatic blood pressure changes were exhibited by 6 patients (1.8% of the total safety population) at any post-baseline visit. Orthostatic hypotension was not reported as an AE by any patient in the study.

Safety in Long-term Study VAA A2201E1

Patient Characteristics and Drug Exposure

In the long-term extension, demographics were not summarized separately for patients who received triple therapy. The total population was 83.0% Caucasian, 7.1% Black and 0.7% Oriental. Approximately 47% of the patients were female and the mean age was 54.2 years, ranging from 20–89 years.

In this long-term extension study, the overall mean exposure to valsartan/amlodipine with or without the addition of HCT was 329 days (median, 364 days). The maximum possible duration of exposure to triple therapy in this study as per protocol was 44 weeks. Overall mean exposure to triple therapy ranged from 181.1-228 days depending on the dose.

A total of 1136 patients were exposed to valsartan/amlodipine with or without the addition of HCT for approximately 6 months and 425 patients were exposed for one year or more. Approximately 90% of patients had at least 270 days of exposure. Similar exposure was achieved in both dose groups at each time interval (6 months, 9 months and one year).

Adverse Events

The overall incidence of adverse events in the total extension population was 76.1% and was comparable in the low dose (74.8%) and high dose (77.4%) groups.

The most frequently reported adverse events were peripheral oedema, nasopharyngitis, dizziness, headache, and back pain. The incidence of peripheral oedema and dizziness appeared to be dose dependent. Most events were mild to moderate in severity, and not suspected to be study drug related. The adverse events and their respective incidence rates were not unexpected in patients treated with an angiotensin receptor blocker and a calcium channel blocker in combination with or without HCT in a forced titration design for a total duration of one year.

While the incidence of peripheral oedema was lower in patients who added HCT to their regimen than in those who remained on valsartan/amlodipine 160/5 or 160/10 mg, this observation must be interpreted cautiously because patients were not randomized to HCT and this population was a select group of patients who had not responded to valsartan/amlodipine.

Deaths, Serious AEs and discontinuations due to AEs

No deaths were reported in this trial. Twenty-three patients (3.7%) in the low dose group, and 26 patients (4.1%) in the high dose group experienced SAEs that had an onset during the extension. The most frequently reported SAEs were gastrointestinal disorders and neoplasms (8 patients in each primary system organ class), musculoskeletal disorders (6 patients), general disorders, hepatobiliary disorders and infections and infestations (4 patients in each). Two patients (0.4%) in the valsartan/amlodipine 160/10 mg group had osteoarthritis classified as serious, and two patients (0.3%) in the valsartan/amlodipine 160/5 mg group had breast cancer. Otherwise, no more than 1 patient (0.2%) in any individual treatment group experienced more than one SAE. A total of 60 patients (4.8%) were discontinued from the study due to adverse events (18 in the low dose group, and 42 in the high dose group). The most frequently reported AE leading to discontinuation was peripheral oedema (13 patients in the high dose group, and 2 patients in the low dose group). Eight of the discontinuations were associated with SAEs.

Vital signs and laboratory changes

Laboratory changes observed with the long-term administration of the combination of valsartan/amlodipine with or without the addition of HCT were consistent with the known effects of each monotherapy agent. Small increases in creatinine and uric acid and decreases in potassium were observed more frequently in patients receiving HCT. The incidence of orthostatic blood pressure changes was: 8.6% in the low dose group and at 10.2% in the high dose group. The vast

majority of cases were isolated. One patient was discontinued due to orthostatic hypotension reported as an adverse event.

Safety Assessment in VAA and VAH Studies

Safety data from each of these six clinical studies are reported individually in the respective Clinical Study Reports, according to the study objectives for the randomized regimens in the study. These studies are very briefly summarized below for completeness. The number of patients exposed to triple therapy is highlighted and the adverse events related to triple therapy are summarised.

Demographics were not summarized separately for patients who received triple therapy in the double-blind valsartan + amlodipine studies, but are summarized for the total population. Mean ages were generally similar across studies, with most patients younger than 65 years old. Studies VAA A2401 and VAA A2403 had more elderly patients than Studies VEA A2302 or VAA A2402. Except for Study VAA A2402, which enrolled only Black patients, most patients were Caucasian. In general, males and females were evenly distributed except for Study VAA A2402, which had 60% females.

Demographics were summarized separately for patients who received triple therapy in Studies VAH BDE13E1 and VAH B2406E1, but are only available for the total open-label population in Study VAH BUS04. Mean ages of the triple therapy patients were generally similar across studies, with most patients younger than 65 years old. Study VAH BDE13E1 had more elderly patients than the other studies. Most patients were Caucasian. Males and females were evenly distributed in Study VEA A2302 and Study VAH BDE13E1, but more males than females were enrolled in Study VAH BUS04 and Study VAH B2406E1.

Study VAA A2401

The overall occurrence of AEs in the subset of patients who received triple therapy was 30.1%. The most frequently reported AEs in the subset of patients treated with triple therapy were peripheral oedema (2.6%), headache (2.0%), and back pain (2.0%).

Study VAA A2402

The overall occurrence of AEs in the subset of patients who received triple therapy was 42.9%. The most frequently reported AEs in the subset of patients treated with triple therapy were peripheral oedema (9.5%), oedema (3.4%), and headache (2.7%)

Study VAA A2403

The overall occurrence of AEs in the subset of patients who received triple therapy was 33.8%. Peripheral oedema (14%) and nasopharyngitis (2.9%) were the most frequently reported AEs in the subset of patients on triple therapy.

Study VAH BUS04

The overall occurrence of AEs in the subset of patients who received triple therapy was 23.6%. The most frequently reported AEs in the subset of patients treated with triple therapy were dizziness (5.6%), pain (2.8%), pain in extremity (2.8%), and hypoesthesia (2.8%).

Study VAH BDE13E1

The overall incidence of AEs in patients taking triple therapy was 10.6%. The most frequently reported AE was nervousness (3.0%). No deaths or SAEs occurred and one patient permanently discontinued study drug in the extension.

Study VAH B2406E1

The overall occurrence of AEs in the subset of patients who received triple therapy in the extension was 21.5%. Not more than one patient (1.3%) experienced any individual AE.

Summary of Safety

In the pivotal, double-blind, controlled study VEA A2302, the overall incidence of AEs regardless of relationship to treatment was similar in patients receiving triple therapy compared to patients receiving dual therapy.

In study VEA A2302 the most common AEs regardless of relationship to treatment in the triple therapy group were dizziness, peripheral oedema, and headache. Dizziness occurred more often with triple therapy (7.7%) and valsartan/HCT (7.0%) than with valsartan/amlodipine (2.3%) or HCT/amlodipine (3.9%). The incidence of peripheral oedema with triple therapy (4.5%) was less than that reported with HCT/amlodipine (8.9%) and valsartan/amlodipine (8.5%) but greater than valsartan/HCT (0.9%). Otherwise, the incidence of AEs with triple therapy was generally comparable with the incidence rates with dual therapy.

In study VEA A2302, other than dizziness, AEs potentially related to low blood pressure either did not occur, or occurred at very low frequencies. Most adverse events were mild to moderate in severity, and not suspected to be study drug related. The most common AEs suspected to be related to study drug in the triple therapy group were dizziness and peripheral oedema with a similar pattern of incidence rates across treatment groups as reported for AEs regardless of relationship to treatment.

In study VEA A2302, triple therapy was well-tolerated regardless of gender, age, race, and diabetes status. The overall incidence of serious AEs and AEs leading to study discontinuation in the valsartan/HCT/amlodipine group was low.

In study VAA A2201E1, no significant new adverse events were observed over 52 weeks of treatment with triple therapy compared to short-term treatment with triple therapy in other studies and to the known effects of the mono-therapy components. Study VAA A2201E1 was conducted over 52 weeks to obtain sufficient long-term safety data for intended doses to be marketed in accordance with current ICH and EU guidelines.

No important new safety issues were identified in the supportive uncontrolled study VEA ABR01 or the ancillary studies where the primary objective was not to evaluate the triple combination.

Clinical Summary and Conclusions

The clinical development program consisted of ten clinical studies, one pivotal and eight supportive studies, to assess efficacy. Of the 10 studies, 9 have been completed

Efficacy

The submission has been evaluated against the *Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, CPMP/EWP/238/95 Rev.2 of the European Agency for the Evaluation of Medicinal Products Human Medicines Evaluation Unit.*

The superiority of triple combination versus double combinations has been demonstrated in the pivotal study VEA 2302 by showing its superiority in reducing blood pressure. The randomization in a double-blind fashion to four arms of the study (>500 patients to each arm) is an adequate strategy to demonstrate that the blood pressure lowering effect of the triple combination is superior to the three possible double combinations. Reduction in blood pressure has usually been accepted as a valid surrogate endpoint in assessing antihypertensive medication. However, a clearly effective marker of superiority would be by demonstrating a positive effect on morbidity and mortality (*EAEMP, Treatment of Hypertension, CPMP/EWP/238/95 Rev.2, Section 2.2*). It is

recommended that until these results are available, it should be specifically mentioned in the Product Information that beneficial effects on mortality and cardiovascular morbidity are unknown.

Pivotal Study VEA 2302 was a parallel group study of the high dose triple combination, 320/25/10 compared with all three possible dual combinations, that is, 320/25, 320/10 and 25/10. It has been taken in consideration that the triple combination is a second line drug and treatment should not be initiated with this fixed dose combination. However, in accordance with *Section 7.2, Second-line therapy of the Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, CPMP/EWP/238/95 Rev.2*, dose finding studies are necessary to identify the appropriate doses for each component of a fixed combination. In the absence of EU guidelines referring to triple therapy, an attempt should be made to extrapolate the requirements referring to dual combinations to the triple combinations. Considering that patients being prescribed triple therapy will have already been on the highest dose of the dual combination, a dose selection study might be considered for the third add-on component only. For example, a dose titration study comparing the efficacy of the lower and higher doses of the third add on component against all possible dual combinations. A further requirement would be to conduct parallel group comparisons of the triple combination with the individual dual combinations, as recommended in *Paragraph 2 of Section 7.2.1 of EAEMP, Treatment of Hypertension, CPMP/EWP/238/95 Rev.2*.

A deficiency of the pivotal study VEA 2302 was that of a short treatment period (8 weeks). Drug therapy in the main dose-response studies should last 2-3 months to demonstrate efficacy (*EAEMP, Treatment of Hypertension, CPMP/EWP/238/95 Rev.2, Study Duration Guidelines, Section 5.4*). However, the results of VEA 2302 did suggest that the triple combination produced statistically significant reductions in blood pressure.

The open-label uncontrolled study VEA ABR01 is the only triple combination add-on study submitted in this submission, and evaluated the add-on effect of an extra 5mg of amlodipine or an extra 12.5mg of HCT for those patients who did not respond to a regimen of 5/160/12.5mg of amlodipine/ valsartan/ HCT. However, it appears that there could have been patients who were only on this add-on therapy for a further 4 weeks before the final assessment. Another important deficiency of this study would appear to be that only patients who did not meet the target BP continued in the study at each titration step. Patients who successfully met the target BP were withdrawn from the study. This means that for these latter patients there are no data available on maintenance of effect (drug therapy in this non-responder group of patients should have been maintained over at least 4 weeks as recommended in *section 5.4 of the Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, CPMP/EWP/238/95 Rev.2*).

The open-label extension of study VAA A2201E1 is the only long term study, which was conducted over 52 weeks to obtain sufficient long-term safety data for intended doses to be marketed in accordance with current ICH and EU guidelines. However, the efficacy results showed that the reduction in mean MSDBP and MSSBP for the high dose triple combination was less than corresponding reductions for the high dose dual combination of valsartan/amlodipine. For the low dose combinations, the reduction of mean MSDBP was again less on triple as compared with the dual combination. For the low dose combinations, only the reduction in mean MSSBP was greater on triple as compared with the dual combinations. Based on the above it is considered that the extension of study VAA A2201E1 has not produced data which indicates a major add-on effect of HCT when added to dual therapy.

Studies [VAA A2401], [VAA A2402], [VAAA2403], [VAH BUS04], [VAH BDE13E1] and [VAH B2406E1] have been included as supportive studies for the submission. Nevertheless, in these studies the subgroup of patients who received triple therapy was not separately evaluated. Hence, these studies did not contribute any efficacy data to this application.

Effects on concomitant diseases have not been well examined. Patients with relevant concomitant conditions like renal disease, ischaemic heart disease, heart failure and cerebrovascular diseases have been excluded from the Pivotal Study. Only Supportive Study CVAA 2402 has included a subgroup of diabetic patients. It would be relevant to obtain information about the effects of the triple therapy on concomitant diseases in hypertensive patients. Furthermore, despite its superior blood pressure lowering effect, the influence of antihypertensive triple drug combination on (cardiovascular) morbidity and mortality was not evaluated.

Withdrawal and rebound effects on the efficacy of Exforge have not been studied separately. As described in the original valsartan monotherapy submissions, no withdrawal or rebound effects on efficacy of valsartan monotherapy have been observed. There is no mention of withdrawal or rebound effects in the prescribing information for HCT or amlodipine. No formal study has been conducted to evaluate this phenomenon with the triple combination of valsartan/HCT/amlodipine.

It is suggested that in the PI it should be specifically mentioned that withdrawal and rebound effects on efficacy of Exforge triple combination have not been studied.

Safety

The clinical summary of safety considered data obtained in 582 hypertensive patients who received triple therapy with valsartan/HCT/amlodipine in the pivotal, double-blind, controlled study and in 960 additional hypertensive patients who received triple therapy in 8 other uncontrolled trials or trials in which the primary objective was not to evaluate the triple combination. At least 247 and up to 271 patients received long term triple therapy. The total number of patients exposed to triple therapy in the safety population was at least 1789 and up to 1813.

A slight discrepancy between the most common adverse events related to the triple-combination therapy exists between the Pivotal and the Supportive Studies. Dizziness is the adverse event having a slightly higher incidence with the triple therapy in the Pivotal Study and the most frequently reported AEs leading to discontinuation were dizziness (15 patients, 0.7%), hypotension (10 patients, 0.4%) and peripheral oedema (8 patients, 0.4%). On the other hand, in the supportive studies which were conducted over a longer time period than the Pivotal Study, the most frequently observed AE related to triple therapy is peripheral oedema. It is speculated that the increased incidence of peripheral oedema may have been related to the introduction of amlodipine. It is also of note that the peripheral oedema incidence was higher in the 'high risk patients' where it could have been related to a pre-existing cardio-vascular condition.

Triple therapy with valsartan/HCT/amlodipine was generally well-tolerated and the observed safety profile was consistent with the known pharmacological effects of an angiotensin receptor blocker, a thiazide diuretic and a calcium channel blocker.

It has been widely accepted by experts that combination therapy is the choice for high risk individuals with hypertension. This has been supported by large Clinical Trials such as ACCOMPLISH, ADVANCE, ASCOT and ONTARGET.[14,15,16,17,18,19]

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[14] Jamerson K, Weber MA, Bakris GL et al. Benazepril plus amlodipine or HCT for hypertension in high-risk patients. N Engl J Med 2008; 359: 2417-2428.

[15] Dahlof B, Sever PS, Poulter NR et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005; 366: 895-906.

[16] Poulter NR, Wedel H, Dahlof B et al. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). Lancet 2005; 366:907-13.

The VALUE trial, conducted on 15,245 high-risk hypertensive patients aged 50 years or older has tested the efficacy and safety of the double combination treatment with valsartan or amlodipine, with HCT as second add-on therapy.[20]

Recommendation

Despite a number of methodological concerns, as discussed, the evaluators consider that on balance, it is reasonable to recommend that Exforge HCT (amlodipine besylate/valsartan/ HCT) 5/160/12.5 mg, 5/160/25 mg, 10/160/12.5 mg, 10/160/25 mg and 10/320/25 mg fixed combination tablets be approved for the treatment of hypertension, as replacement therapy in patients whose blood pressure is adequately controlled on amlodipine, valsartan and HCT, used as individual or combination therapies.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

Approval was recommended from a chemistry, quality control and bioavailability aspect and a number of issues were brought to the attention of the clinical delegate by the pharmaceutical evaluator.

Four bioavailability studies and a food effect study were provided. As noted by the pharmaceutical evaluator, each study used an appropriate study design and appropriately validated test methods for the assessment of the various component drugs. Bioequivalence was demonstrated satisfactorily between the fixed-dose combination and the component monotherapies for AUC. In one study there were slightly equivocal findings for valsartan with respect to C_{max} but the Delegate does not view them as clinically significant.

There was no bioavailability data specifically presented for the fixed-dose combinations of 5/160/25, 10/160/12.5 and 10/320/25 mg but an adequate justification for omitting such studies was submitted.

As noted by the pharmaceutical evaluator, the Dosage and Administration section of the proposed PI states that the fixed-dose combination tablet may be taken with or without food and the Pharmacokinetics section states that the AUC of valsartan is reduced by 48% with food. There appears to be an inconsistency between these two statements. Furthermore, the stated 48% reduction in AUC with food is inconsistent with the results of the food study (VEA489A 2310) which demonstrated a 14% increase in the value of the AUC of valsartan with food. The sponsor

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[17] Patel A, MacMahon S, Chalmers J et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007; 370:829-40.

[18] The ONTARGET investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008; 358:1547-1559.

[19] Mann JF, Schmieder RE, McQueen M et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet 2008; 372: 547-53.

[20] Julius S, Kjeldsen SE, Weber M et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004; 363: 2022-31.

was asked to comment on these inconsistencies and propose suitable amendments to the PI which clarify the issue.

There were variable PK interactions between each of the components. However, none was clinically significant. The Delegate supported the recommendations made by the pharmaceutical evaluator with regard to PI amendments.

Nonclinical

There are no nonclinical objections to the registration of the proposed two new strengths in combination.

The nonclinical data submitted by the sponsor consisted of GLP-compliant bridging toxicology and toxicokinetic studies in rats of up to 13 weeks duration. This was noted to be an appropriate data package for a fixed combination of previously approved components.

No genotoxicity, carcinogenicity or reproductive toxicity studies were submitted which is acceptable and consistent with ICH guidelines for fixed dose combinations using previously approved components. As noted in the PI, Exforge HCT should not be used in pregnancy due to the known effects of angiotensin receptor blockers in the second and third trimesters of pregnancy.

The nonclinical evaluator observed that there were no significant pharmacokinetic interactions or novel toxicities noted for the triple combination in a well-conducted, GLP-compliant, 13 week, oral, bridging toxicology study in rats.

The nonclinical evaluator further commented that the toxicities observed were well known, reversible, "class" effects and reflected target organ toxicities which can be monitored clinically.

Clinical

There was a single study, VAL489A0017, in 297 patients with mild to moderate hypertension which examined the efficacy of valsartan in fasted and fed subjects over 12-14 weeks. Studies specifically designed to evaluate the pharmacodynamics of the fixed combination of amlodipine/valsartan/HCT were not performed.

To examine the pharmacokinetics of Exforge HCT, there were nine (9) human studies, comprising 275 subjects (164 healthy and 111 patients with hypertension)

The clinical development program consisted of 10 clinical studies, 9 of which have been completed. Two completed studies, VEA A2302 and VEA ABR01, were designed to assess the efficacy and safety of the amlodipine/valsartan/HCT combination. There was one long-term, open-label extension trial, VAA A2201E1, designed to evaluate the dual combination amlodipine/valsartan with the optional addition of HCT. The remaining 6 completed studies, VAA A2401, VAA A2402, VAA A2403, VAH BUS04, VAH BDE13E1 and VAH B2406E1, were designed to evaluate various dual combination regimens. None of these six studies contained any evaluable data relating to the efficacy of the triple combination. The Delegate requested that the sponsor clarify both the identity and role of the tenth study which is ongoing and furthermore, indicate when the sponsor proposes submitting the data from this study (or is the discrepancy due to Study VAA A2201 and its long-term extension)?

The clinical evaluator has recommended that Exforge HCT fixed-combination tablets be approved for the treatment of hypertension as replacement therapy in patients whose blood pressure is adequately controlled on amlodipine, valsartan and HCT, used as individual or combination therapies.

Pharmacology

Pharmacodynamics

The double-blind portion of the 12-14 week trial, VAL489A0017, consisted of an 8-week treatment period with patients receiving 80 mg valsartan in a fasted or fed state or placebo. Valsartan 80 mg, in both fasted and fed groups, was significantly superior at reducing trough mean diastolic blood pressure both at end point and visit 7 (Week 12). It is worth noting that while there was no significant difference in anti-hypertensive response between the fed and fasted groups, the mean reduction in blood pressure in the fasted group was numerically greater by 1.8 mm Hg than that in the fed group.

Pharmacokinetics

No studies examined the pharmacokinetics of Exforge HCT in special populations of subjects such as the elderly or subjects with hepatic or renal dysfunction.

The rates and extents of absorption of the components of the fixed combination of valsartan/HCT/amlodipine were equivalent to those for each of the separate monotherapies.

According to the clinical evaluator, there is evidence that valsartan decreases the exposure of HCT by up to 31%. However, there was no evidence of clinically significant drug-drug interactions when the drugs were administered as dual combinations (valsartan and HCT; valsartan and amlodipine) versus the component monotherapies. There were no PK data provided for the co-administration of amlodipine and HCT although because of differences between these two drugs in T_{max} and the routes of elimination, any interaction is less likely. The absence of any clinically significant drug-drug interactions was also demonstrated by the results of Study VEA 489A2104 which assessed pharmacokinetics in the target population (evaluated by both the clinical and pharmaceutical evaluators).

Efficacy

Pivotal Study **VEA A2302** was a parallel group study which evaluated the efficacy and safety of once-daily treatment with the triple combination of valsartan/HCT/amlodipine 320/25/10 mg compared to 3 dual therapies: valsartan/HCT 320/25 mg, valsartan/amlodipine 320/10 mg and HCT/amlodipine 25/10 mg. The primary efficacy variables were the changes from baseline to endpoint in MSDBP and in MSSBP. At endpoint, after 8 weeks of double-blind treatment, a clinically and statistically significantly greater reduction of 24.6 mmHg in MSDBP was achieved with triple therapy, while there were reductions of 19.5 to 21.5 mm Hg with the 3 dual combination treatments (all reductions compared with baseline, $p < 0.0001$) (Table 10). Secondary efficacy results were consistent with those for the primary parameter.

Study **VEA ABR01** was a randomized, open-label, multicentre, two-arm, parallel group study with 340 patients enrolled into the dual therapy (valsartan/HCT) run-in phase of whom 326 (95.9%) completed this phase of the study. Then 264 patients entered the low-dose triple combination therapy phase (valsartan/HCT/amlodipine 160/12.5/5 mg and of these 182 patients subsequently entered the randomized 2-arm triple combination therapy phase. The objective of the study was to estimate the proportion of patients not controlled on the dual combination of valsartan/HCT who reached blood pressure control after 12 weeks of treatment with a valsartan/HCT/amlodipine triple combination. It should be noted that due to lower than expected blood pressure control rates, the enrolment stopped at 340 patients.

The evaluator that for all ITT patients who received triple therapy, the proportion of patients who achieved blood pressure control at endpoint (week 12) was 61.0%. The Delegate requested that the sponsor clarify from where this result was derived and how it corresponds to overall blood pressure control percentages in the mid-forties (see next sentence). The overall blood pressure control rates

at week 12 were similar for both randomized treatments (43.9% for valsartan/HCT/amlodipine 160/12.5/10 mg and 45.8% for valsartan/HCT/amlodipine 160/25/5 mg) (Table 15).

Clinically relevant reductions in sitting blood pressure were achieved at all time points with all triple therapy regimens.

Study **VAA A2201E1** was a 52-week, multicentre, open-label extension study to Protocol 2201 in 1300 patients with mild to moderate uncomplicated essential diastolic hypertension, the primary objective of which was to further evaluate the safety, tolerability and long-term efficacy of once daily administration of the combination of valsartan/amlodipine 80/2.5, 80/5, 160/5 or 160/10, alone or in combination with HCT 12.5 mg. The study was completed as planned in 1300 patients who successfully completed 8 weeks of double-blind treatment in Protocol VAA A2201 without serious ADRs. Patients with a MSDBP < 90 mm Hg and a MSSBP < 140 mm Hg wishing to continue treatment with valsartan/amlodipine were eligible to enter this 52-week open-label extension. After the 8 weeks of double-blind treatment, patients were then randomized in an open-label fashion to receive either valsartan/amlodipine 80/2.5 mg once daily (low-dose group) or 80/5 mg once daily (high dose group) for a period of 4 weeks. Subsequently, patients without symptomatic hypotension or significant peripheral oedema were force titrated to valsartan/amlodipine 160/5 mg once daily (low dose group) or 160/10 mg once daily (high dose group), for the remainder of the trial. Patients whose MSDBP remained ≥ 90 mm Hg or whose MSSBP remained ≥ 140 mm Hg could have added HCT 12.5 mg. Patients who experienced intolerable AEs at any time following up-titration could be back-titrated to a prior dose combination of valsartan/amlodipine, with or without HCT.

The Delegate noted that it was almost impossible to determine what exact dosage groups were being compared in this study and this will be discussed later. The results for this study were negative and the Delegate considered whether this was in part due to the overly complicated design of the study. The Delegate requested that the sponsor clarify in some detail the findings of this study. The efficacy results for this study showed that for the high dose triple combinations (160/10/12.5 mg or 80/5/12.5 mg), the reductions in mean MSDBP and MSSBP were less than for the corresponding reductions for the high dose dual combinations of valsartan/amlodipine, 160/10 or 80/5 mg. For the low dose combinations, only the reduction in the mean MSSBP was greater on the triple combinations (160/5/12.5 mg or 80/2.5/12.5 mg) as compared with the dual combinations (160/5 or 80/2.5 mg) (Table 17).

There were six other completed studies. They involved exposure to the triple combination through the double-blind or optional open-label addition during the late phase of the study of HCT to the dual combination valsartan/amlodipine (Studies VAA A2401, VAA A2402 or VAA A2403) or of amlodipine to the dual combination of valsartan/HCT (Studies VAH BUS04, VAH BDE13E1 or VAH B2406E1) or of valsartan to the dual combination of amlodipine/HCT (Study VAH B2406E1). Efficacy was not evaluated in the subgroups of patients who received the triple combination in any of these trials and hence they can make no meaningful contribution to the efficacy debate. They will not be considered further from the point of view of efficacy.

Safety

The sponsor presented safety data from all studies. The total number of patients exposed to triple therapy in the safety population was at least 1789 and up to 1813.

In the pivotal, double-blind, controlled study VEA A2302, the overall incidence of AEs regardless of relationship to treatment was similar in patients receiving triple combination therapy compared to patients receiving dual combination therapy.

In study VEA A2302 the most common AEs regardless of relationship to treatment in the triple therapy group were dizziness, peripheral oedema, and headache. Dizziness occurred more often with triple therapy (7.7%) and valsartan/HCT (7.0%) than with valsartan/amlodipine (2.3%) or

HCT/amlodipine (3.9%). The incidence of peripheral oedema with triple therapy (4.5%) was less than that reported with HCT/amlodipine (8.9%) and valsartan/amlodipine (8.5%) but greater than valsartan/HCT (0.9%). Otherwise, the incidence of AEs with triple therapy was generally comparable with the incidence rates with dual therapy.

In study VEA A2302, other than dizziness, AEs potentially related to low blood pressure either did not occur, or occurred at very low frequencies. Most adverse events were mild to moderate in severity, and not suspected to be study drug related. The most common AEs suspected to be related to study drug in the triple therapy group were dizziness and peripheral oedema with a similar pattern of incidence rates across treatment groups as reported for AEs regardless of relationship to treatment.

In study VEA A2302, triple therapy was well-tolerated regardless of gender, age, race, and diabetes status. The overall incidence of serious AEs and AEs leading to study discontinuation in the valsartan/HCT/amlodipine group was low.

In study VAA A2201E1, no significant new adverse events were observed over 52 weeks of treatment with triple therapy compared to short-term treatment with triple therapy in other studies and to the known effects of the mono-therapy components. Study VAA A2201E1 was conducted over 52 weeks to obtain sufficient long-term safety data for intended doses to be marketed in accordance with current ICH and EU guidelines. Over 550 patients in each of the low and high dose regimens were exposed for at least 6 months and over 200 patients in each of the low and high dose regimens were exposed for at least 12 months. These numbers meet the requirements for 300 patients exposed for 6 months and 100 patients for 12 months.

No significant new adverse events were observed with long-term treatment compared to short-term treatment. Overall, no new significant safety signals appeared in the studies submitted for evaluation.

Summary of Evaluators' Recommendation

The clinical evaluators have identified a number of methodological concerns related to the studies submitted in the submission and the Delegate will consider these in the risk/benefit discussion below. Despite these concerns, the clinical evaluators consider that, on balance, it is reasonable to recommend that the combination tablets be approved for the treatment of hypertension, as replacement therapy in patients whose blood pressure is adequately controlled on amlodipine, valsartan and HCT, used as individual or combination therapies.

Response to the TGA Clinical Evaluation Report by the Sponsor

The sponsor notified the TGA of errors of fact identified in the Exforge HCT clinical evaluation report. Those errors have been corrected in this AusPAR.

Risk-Benefit Analysis

Efficacy

The most relevant EU guideline is CPMP/EWP-238/95 Rev. 2, *Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension*. For any claim of second-line therapy for example, it is usually necessary to establish the following:

- a statistically significant and clinically relevant additional blood pressure reduction on the fixed-dose combination in those patients who did not respond adequately to standard therapeutic doses of either monotherapy
- demonstration of statistically significant superior efficacy of the fixed-dose combination with no additional safety concerns outweighing the additional benefits of the fixed-dose

combination from a parallel group comparison of the fixed-dose combination with the individual components at the same therapeutic doses.

However, the sponsor has clarified in its letter to the TGA that Exforge HCT is "proposed to be indicated as replacement therapy only" – the latter are the actual words used in the sponsor's letter.

The pivotal study, VEA A2302, was a parallel group study of the high dose triple combination, 320/10/25, compared with all possible dual combinations, 320/10, 320/25 and 10/25 and superiority of that triple combination versus the three possible dual combinations in reducing blood pressure was demonstrated. Now apart from the second study in the submission, VEA ABR01, there were no studies of add-on therapy and dose-titration of the third drug. Furthermore, there were no studies at all, either parallel or add-on, of any of the proposed lower dosage strength triple combinations. As noted by the clinical evaluator, because patients being prescribed triple therapy will have already been on the highest dose of the dual combination, it would be important to conduct a dose selection study for that third add-on component. However, it should also be noted that the latter scenario is not part of the indication sought by the sponsor for this triple combination. The indication which has been sought is for replacement therapy and for replacement therapy only. A clear deficiency of the pivotal study was its short treatment period of 8 weeks as opposed to the more standard 12 weeks.

The open-label, uncontrolled study, VEA ABR01, is the only triple combination add-on study submitted in the submission. It evaluated the add-on effect of an extra 5 mg of amlodipine or an extra 12.5 mg of HCT for those patients who did not respond to a regimen of amlodipine/valsartan/HCT 5/160/12.5 mg. As already noted by the clinical evaluator, it appears that there could have been patients in this study who were only on the add-on therapy for a total of 4 weeks only before the final assessment. Also patients who were found to have met the target BP at each titration step were withdrawn from the study which means that for these patients there are no data available on maintenance of effect. The enrolment in this study was stopped at 340 patients due to lower than expected blood pressure control rates. The trial was uncontrolled and not designed to compare the two groups of triple therapy (160/10/12.5 mg versus 160/5/25 mg) or to compare triple therapy with dual therapy. The sponsor was asked to comment on these issues. The sponsor was also asked to comment on the result that, for all ITT patients who received triple therapy, the proportion of patients who achieved blood pressure control at endpoint (week 12) was 61.0%. In particular, how does the latter result accord with results of 43.9% and 45.8% for rates of blood pressure control in each of the randomized treatment arms?

The open-label extension study, VAA A2201E1 was the only long-term study and was conducted over 52 weeks. It was a voluntary extension study without pre-defined statistical testing. The efficacy results showed that the reduction in mean MSDBP and MSSBP for the high dose triple combinations were less than the corresponding reductions for the high dose dual combinations of valsartan/amlodipine. For the low dose combinations, the reduction in mean MSDBP was again less on triple as compared with the dual combinations. For the low dose combinations, only the reduction in mean MSSBP was greater on triple as compared with the dual combinations. The Delegate indicated that he has had difficulty interpreting the efficacy results of this study and had a number of specific questions to ask of the sponsor.

- In the original 8-week study, A2201, were the patients randomized into <u>four</u> dosage strength groups, namely 80/2.5, 80/5, 160/5 or 160/10 of the dual combination valsartan/amlodipine?
- In the results reported in Table 17, there are 115 people shown as having taken high dose triple combination therapy. What precise doses were these people taking? According to the study design, they could have been taking either valsartan/amlodipine/HCT 160/10/12.5 or 80/5/12.5. Is this correct?

- By contrast there are 506 people who are shown as taking high dose dual combination therapy. Once again, according to the study design, these people could have been taking either valsartan/amlodipine 160/10 or 80/5. Is this correct?
- A similar pair of questions could be asked concerning the comparison of the low dose triple and dual combination therapies (in 154 and 462 subjects, respectively).

The sponsor was requested to respond to all these questions. If what the Delegate has assumed about the dosage strengths being taken is true, then it is not surprising that the efficacy results did not demonstrate an additive benefit of HCT, for in each group being compared, there were two different dosage strength regimens. The sponsor was asked to give a critical appraisal of the design of this study. The Delegate was of the opinion that this extension study has not provided any evidence of extra treatment benefit when HCT is added to dual therapy.

As noted by the evaluators, effects on and of concomitant diseases have not been well examined in this submission. Patients with relevant concomitant conditions such as renal disease, ischaemic heart disease, heart failure and cerebrovascular diseases were excluded from the pivotal study. Only supportive study VAA A2402 included a sub-group of diabetic patients but there were no studies of the efficacy of the triple combination in any of the 6 supportive studies.

Safety

Studies found that triple therapy with valsartan/HCT/amlodipine was generally well tolerated and the observed safety profile was consistent with the known pharmacological effects of an angiotensin receptor blocker, a thiazide diuretic and a calcium channel blocker. Satisfactory evidence of long-term safety was provided by the open-label extension study VAA A2201E1.

Summary

There were a number of methodological flaws in the studies in this submission. The pivotal study did not evaluate any of the proposed lower dosage strength triple combination therapies. However, it did demonstrate superiority of the 320/10/25 triple combination over all three possible dual combinations. There was only one add-on study in the submission but this did not examine the add-on effect of valsartan. This latter study was also compromised by the fact that subjects could have been on final treatment for at most 4 weeks and that there was flawed data on maintenance of effect. Most importantly, the third study, the long-term extension study failed to demonstrate an add-on effect of HCT when added to dual therapy. These deficiencies in the data set would not have permitted any approval for second-line therapy. Because of these multiple flaws, the Delegate was of the opinion that there was sufficient evidence of efficacy but only to support a very restricted indication, namely the indication sought for replacement therapy but only for the latter. The indication will have to specify that is only approved for this purpose. For example there is insufficient evidence in the submission to support any possible implication of approval for add-on or step-up therapy for someone who is already on a dual combination. The PI will have to be quite explicit about this.

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

Exforge HCT is indicated ONLY as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of amlodipine, valsartan and HCT taken as either three single-component formulations or as a dual-component formulation with a single-component formulation, all components at the same dose level. Treatment should not be initiated with this combination (see Dosage and Administration)

The sponsor should include the following issues in their pre-ADEC response:

- clarification of the issue of the actual level of reduction of the AUC of valsartan with food, especially in the fixed-dose combination tablet and how this will be precisely addressed in the PI
- clarification of the identity and role of the tenth clinical study which as yet remains incomplete and of the sponsor's intentions about submission of data from this study
- clarification of the source of the result for the study VEA ABR01 that for all ITT patients who received triple therapy, the proportion of patients who achieved blood pressure control at endpoint (week 12) was 61.0% and how this result accords with the quoted overall blood pressure control rates for both randomized treatments, results which were in the mid-forties.
- clarification of the statement in the evaluation reort that the number of patients exposed to triple therapy in the safety population was at least 1789 and up to 1813 – why isn't the exact figure known?
- the request of the Delegate for answers to a number of questions about the open-uncontrolled study, VEA ABR01 and the open-label extension study VAA A2201E1 which have been noted earlier in the Risk/Benefit discussion.

Response from the Sponsor

A food effect bioavailability study was conducted with Exforge HCT tablet [VEA489A2310]. The study results indicated that the C_{max} and AUC of valsartan is 12% and 14% higher under fed conditions as compared to fasted state condition with 90% confidence intervals falling slight outside of the bioequivalence range of 0.8 to 1.25. The upper limit of 90% confidence interval for C_{max} and AUC was 1.29 and 1.31, respectively. Considering the magnitude of variability of the pharmacokinetic profile of valsartan (up to 44%) in the study, the observed increase in C_{max} and AUC under fed conditions is not considered clinically relevant. In addition, the 90% confidence intervals for both C_{max} and AUC of amlodipine and HCT were within the bioequivalence range of 0.8 to 1.25 indicating that food has no affect on the bioavailability of these drugs from the Exforge HCT tablet. In summary, based on these results it was concluded that the rate and extent of absorption of all three drugs, valsartan, amlodipine and HCT were not altered in the presence of food. The discussion on the PI is outside the scope of this AusPAR.

Study VAA489AUS01 was referred to as an ongoing study in the submission and has subsequently been completed. A multicenter, prospective, randomized, open-label study with blinded outcome evaluation to evaluate the effects of systolic blood pressure lowering to different targets (< 130 mm Hg versus < 140 mmHg) on diastolic function using valsartan and amlodipine in patients with hypertension and diastolic dysfunction. The primary objective was to evaluate the effects of valsartan and amlodipine on the change from baseline in lateral mitral annular myocardial relaxation velocity (E') after 24 weeks of treatment in patients with hypertension and echocardiographic evidence of diastolic dysfunction in lateral mitral annular myocardial relaxation velocity. The study design allowed add-on of other anti-hypertensive agents (including HCT) and as such the study provides additional information on the triple combination. This phase IV study was however never intended to formally support registration of Exforge HCT and will therefore not be submitted to the TGA for formal evaluation. The final Clinical Study Report is however available upon request.

The primary objective of Study VEA ABR01 was to estimate the proportion of patients reaching blood pressure (BP) control after 12 weeks of treatment with a valsartan/HCT and amlodipine treatment algorithm in hypertensive patients not controlled with valsartan/HCT. Two triple combination treatment algorithms were compared and non-responders from both groups continued in the study to achieve the highest dosage of the triple combination (See Figure 1in this AusPAR). Only patients who did not meet target BP continued in the study at each titration-step. Patients who

successfully met the target BP were withdrawn from the study. The calculations of control rate at endpoint and at week 12 are explained in Tables 20 and 21.

Table 20: Control rate at endpoint

Patients (N)	n#	BP controlled at endpoint*	Control rate at endpoint (= BP controlled /n)
264	264	161	61.0% (=161/264)

* BP controlled at endpoint = total patients controlled at Week 4 (5/160/12.5 treatment group), Week 8 (10/160/12.5 and 5/160/25 treatment regimens), and
Week 12 (10/160/12.5 and 5/160/25 treatment regimens) = 60 + (21+18) + (29+33) = 161; # n = total patients received triple therapy

Table 21: Control rate at week 12

Treatment group (N)	n#	BP controlled at Week 12*	Control rate at Week 12 (= BP controlled at Week 12 /n)
10/160/12.5 (N=88)	66	29	43.9% (=29/66)
5/160/25 (N=94)	72	33	45.8% (=33/72)

n = number of ITT patients with non-missing measurements at week 12

In the sponsor's Clinical Summary of Safety, it was noted that 24 patients in Study VAA A2201E may have been counted in two different treatment groups (6 patients in the valsartan/HCT/amlodipine 80/12.5/2.5 mg group may also have been included in the 160/12.5/5 mg group, and 18 patients in the 80/12.5/5 mg group may also have been included in the 160/12.5/10 mg group). Therefore, at least 247 and up to 271 patients were noted as being exposed to triple therapy in this study. This equated to at least 1789 and up to 1813 in the total safety population. Novartis statisticians have since then determined by database review that exactly 267 patients were exposed to triple therapy in Study VAA A2201E and a total of 1809 patients were exposed to triple therapy in all studies (2 of the 6 patients in the 80/12.5/2.5 mg group also took 160/12.5/5 mg, and 2 of the 18 patients in 80/12.5/5 mg group also took 160/12.5/10 mg and had therefore been counted twice).

Study VEA ABR01 was conducted in Brazil and designed to provide efficacy and safety data for a treatment algorithm strategy based on the combination valsartan, HCT and amlodipine in hypertensive patients previously treated with valsartan and HCT and remaining uncontrolled. A naturalistic approach was taken comparing two different possible ways to achieve a higher dosage of the triple combination, that is, 160 mg of valsartan and 25 mg of HCT with amlodipine 10 mg (Figure 1). The primary intent was to mimic clinical practice providing clinicians with information regarding alternative titration schemes for treating their patient. The study was not intended to serve as a pivotal efficacy trial and is classified as a supportive study within the submission and provides additional safety information in a design that evaluates patients not responding to dual therapy.

During the run in phase, a greater number of patients than originally predicted failed to respond to dual therapy. As a consequence, the enrolment of this study stopped at 340 patients. This should however have no impact on the results and conclusions from this study. The pre-specified primary objective of this study was to estimate the proportion of patients reaching blood pressure (BP) control after 12 weeks of treatment with a valsartan, HCT and amlodipine treatment algorithm in hypertensive patients not controlled with valsartan/HCT. Two triple combination treatment algorithms were compared and non-responders from both groups continued in the study to achieve the highest dosage of the triple combination.

Pre-specified secondary objectives included the estimation of control rates, responder rates and changes from baseline in mean sitting diastolic and systolic BP at Week 8, a time point occurring 4 weeks after randomization where the two groups of triple therapy (10/160/12.5 mg versus 5/160/25 mg) could be compared. However Novartis acknowledged that no comparisons can be made between the triple therapy and dual therapy in this design.

As noted by the Clinical Evaluator, there are patients in this study who were on the add-on therapy for a total of only 4 weeks before the final assessment. In addition, patients who met target BP at each titration step were withdrawn from the study and, for these patients, no data are available on maintenance of effect. It is acknowledged that this is a limitation of Study VEA ABR01. No clinical data or conclusions related to Study VEA ABR01 are included in the proposed PI.

The core 8-week **Study VAA A2201** was a randomized, double-blind, placebo controlled, multifactorial, parallel group trial in mild to moderate hypertensive patients. Eligible patients were randomized in equal proportions to one of 15 treatments administered once daily: valsartan monotherapy 40 mg, 80 mg, 160 mg, or 320 mg; amlodipine monotherapy 2.5 mg, or 5 mg; the combination of valsartan/amlodipine 40/2.5 mg, 40/5 mg, 80/2.5 mg, 80/5 mg, 160/2.5 mg, 160/5 mg, 320/2.5 mg, 320/5 mg or placebo. Patients randomized to the valsartan/amlodipine 320/5 mg treatment group began treatment with valsartan/amlodipine 160/2.5 mg for one week before forced titration to the 320/5 mg dose.

The open-label extension study, VAA A2201E1 was the only long-term study submitted with this application and was conducted over 52 weeks. It was a voluntary extension study without pre-defined statistical testing.

The Delegate correctly noted that patients taking high dose dual combination therapy (N=506) could have been taking either valsartan/amlodipine 160/10 or 80/5 and the patient population (N=115) in the high dose triple combination group dose could have been taking either valsartan/amlodipine/HCT 160/10/12.5 mg or 80/5/12.5 mg. Patients were initially randomized in an open-label fashion to receive either valsartan/amlodipine 80/2.5 mg (low dose group) or 80/5 mg (high dose group) for four weeks. Subsequently, patients tolerating therapy were force titrated to valsartan/amlodipine 160/5 mg (low dose group) or 160/10 mg (high dose group), respectively. Patients with BP $\geq$ 140/90 mmHg at any dose following the initial titration period could have HCT 12.5 mg added.

Similarly patients taking low dose dual combination therapy (N=462) could have been taking either valsartan/amlodipine 160/5 or 80/2.5 and patients (N=154) in the low dose triple combination group dose could have been taking either valsartan/amlodipine/HCT 160/5/12.5 mg or 80/2.5/12.5 mg.

Patients who experienced intolerable adverse experiences at any point following up-titration to the higher doses could be back titrated to a prior dose combination of valsartan/amlodipine, with or without HCT.

Due to the permitted back titration, it is not possible to calculate the precise doses taken by all patients. However, within each dose group, the vast majority of patients were successfully force titrated after 4 weeks and most remained on this regimen for the duration of the extension period. Therefore, the majority of patients in the high dose triple combination dose group were receiving valsartan/HCT/amlodipine 160/12.5/10 mg (N=97) compared to 80/12.5/5 mg (N=18) and the majority of patients in the low dose triple combination dose group were receiving valsartan/HCT/amlodipine 160/12.5/5 mg (N=150) compared to 80/12.5/2.5 mg (N=6).

Novartis acknowledged the limitations of the study as outlined by the Delegate. This study was designed to evaluate the long term safety and efficacy of valsartan/amlodipine dual therapy with or without the addition of HCT. Patients were not randomized to triple therapy and no direct comparison to dual therapy should be made.

The Delegate noted that the efficacy results showed that the reduction in mean MSDBP and MSSBP for the high dose triple combinations were less than the corresponding reductions for the high dose dual combinations of valsartan /amlodipine. For the low dose combinations, the reduction in mean MSDBP was again less on triple as compared with the dual combinations. For the low dose combinations, only the reduction in mean MSSBP was greater on triple as compared with the dual combinations. This is not completely unexpected in a selected population whose BP may have been more difficult to control as documented by the slightly higher baseline BP in this population.

Within each treatment group (both high and low dose) where HCT was added at Week 8 (or thereafter), clinically relevant additional reductions in both mean sitting systolic BP (MSSBP) and mean sitting diastolic BP (MSDBP) were observed at all time points subsequent to Week 8 . These data provide support that an extra treatment benefit is achieved when HCT is added to dual therapy.

Advisory Committee Recommendation

The Advisory Committee on Prescription Medicines (ACPM) (formerly ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal, and recommended the following indications:

Exforge HCT is indicated ONLY as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of amlodipine, valsartan and HCT taken either as three single-component formulations or as a dual-component formulation with a single-component formulation, all components at the same dose level. Treatment should not be initiated with this combination. (see Dosage and Administration).

In making this recommendation, the ACPM agreed with the Delegate that the safety and efficacy of the product have been satisfactorily established for this indication.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Exforge (and Ejocia) HCT 5/160/12.5, Exforge (and Ejocia) HCT 5/160/25, Exforge (and Ejocia) HCT 10/160/12.5, Exforge (and Ejocia) HCT 10/160/25 and Exforge (and Ejocia) HCT 10/320/25 tablets containing amlodipine besylate / valsartan / hydrochlorothiazide 5/160/12.5 mg, 5/160/25 mg, 10/160/12.5 mg, 10/160/25 mg and 10/320/25 mg for:

ONLY as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of amlodipine, valsartan and hydrochlorothiazide taken either as three single component formulations or as dual-component formulation with a single component formulation, all components at the same dose level. Treatment should not be initiated with these fixed-dose combinations (see "Dosage and Administration").

Attachment 1. Product Information

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

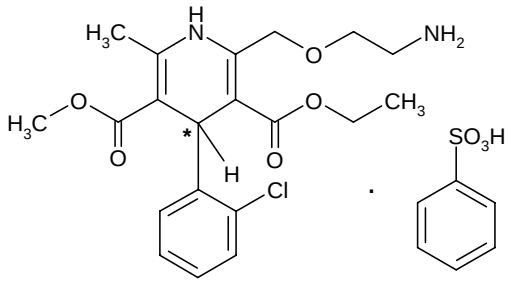
EXFORGE HCT 5/160/12.5®
EXFORGE HCT 5/160/25®
EXFORGE HCT 10/160/25®
EXFORGE HCT 10/160/12.5®
EXFORGE HCT 10/320/25®

(amlodipine besylate/valsartan/hydrochlorothiazide)

NAME OF THE MEDICINE

Active ingredients (INN): amlodipine besylate, valsartan and hydrochlorothiazide

Structural formula:



and enantiomer

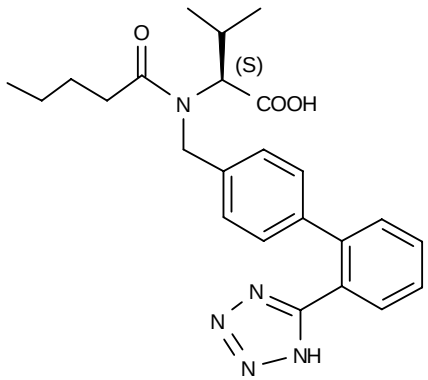
Amlodipine (as the besylate salt)

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

CAS: 111470-99-6

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

Molecular weight: 567.06



Valsartan

(N-Pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4ylmethyl]-L-valine)
CAS : 137862-53-4

Molecular formula: $C_{24}H_{29}N_5O_3$

Molecular weight: 435.5

Hydrochlorothiazide

(6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide -1,1-dioxide)
CAS : 58-93-5
Molecular formula: $C_7H_8ClN_3O_4S_2$

Molecular weight: 297.72

DESCRIPTION

Amlodipine besylate is a white or almost white powder that is slightly soluble in water and sparingly soluble in ethanol. Valsartan is a white to practically white microcrystalline and slightly bitter tasting powder. It is soluble in ethanol and methanol and slightly soluble in water. Hydrochlorothiazide is a white or almost white powder, very slightly soluble in water and freely soluble in dimethylsulfoxide.

Exforge HCT 5/160/12.5®, Exforge HCT 5/160/25®, Exforge HCT 10/160/12.5®, Exforge HCT 10/160/25®, and Exforge HCT 10/320/25® are available as film-coated tablets in five strengths containing amlodipine besylate (5 or 10 mg), valsartan(160 or 320 mg) and hydrochlorothiazide (12.5 or 25 mg) as: 5/160/12.5 mg, 5/160/25 mg, 10/160/12.5 mg, 10/160/25mg and 10/320/25 mg.

Excipients: Cellulose microcrystalline, crospovidone, silica - colloidal anhydrous, magnesium stearate, hypromellose, titanium dioxide, macrogol 4000, purified talc, yellow iron oxide (except 5/160/12.5 mg) and red iron oxide (10/160/12.5 mg only).

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: dihydropyridine derivatives (amlodipine) combinations with angiotensin II antagonists, plain (valsartan) and thiazide diuretics (hydrochlorothiazide).

Exforge HCT combines three antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class, valsartan to the angiotensin II (Ang II) antagonist class and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine

The amlodipine component of Exforge HCT inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans.

In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Valsartan

Valsartan is an orally active, potent and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. The AT_2 receptor subtype has not been definitely shown to be associated with cardiovascular homeostasis. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has about a 20,000-fold greater affinity for the AT_1 receptor than for the AT_2 receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with cough. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($P < 0.05$) less in patients treated with valsartan than in those treated with an ACE inhibitor (2.4 % versus 7.9 %, respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5 % of trial subjects receiving valsartan and 19.0 % of those receiving a thiazide diuretic experienced cough compared with 68.9 % of those treated with an ACE inhibitor ($P < 0.05$).

Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate. In most patients after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours and the peak reduction in blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dose administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy.

Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

Hydrochlorothiazide

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high affinity receptor in the renal cortex with the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na^+Cl^- symporter which affects mechanisms of electrolyte reabsorption. Inhibition of the Na^+Cl^- symporter directly increases excretion of sodium and chloride in approximately equivalent amounts. It also indirectly reduces plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

Pharmacokinetics

Amlodipine

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

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

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

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

Valsartan

Peak plasma concentrations are reached 2 to 4 hours after dosing. The amount absorbed varies widely. Mean absolute bioavailability is 23% and the bioavailability relative to an oral solution is 59%.

The pharmacokinetics of valsartan are linear over the dose range 80 - 320 mg. There is no change in the kinetics of valsartan on repeated administration and little accumulation when dosed once daily. Plasma concentrations are similar in males and females.

When valsartan is given with food, the area under the plasma concentration-time curve (AUC) of valsartan is reduced by 48% although, from about 8 h post dosing, plasma valsartan concentrations are similar for the fed and fasted group.

Valsartan is highly bound to serum protein (94-97%), mainly serum albumin. Steady-state volume of distribution is low (about 17 L) indicating that valsartan does not distribute into tissues extensively.

Valsartan does not undergo extensive biotransformation. Only approximately 25% of absorbed drug is metabolised. The primary metabolite is valeryl 4-hydroxy valsartan, which is pharmacologically inactive. The enzyme(s) responsible for valsartan metabolism have not been identified.

Valsartan shows bi-exponential decay kinetics with a $t_{1/2}\alpha$ of about 1h and a $t_{1/2}\beta$ of about 9.5 hours. After oral dosing, 83% of the dose is excreted in the faeces and 13% in the urine, mainly as unchanged compound. Following intravenous administration, renal clearance of valsartan accounts for about 30% of total plasma clearance. Plasma clearance is relatively slow (about 2 L/h) when compared with hepatic blood flow (about 30 L/h).

Hydrochlorothiazide

The absorption of hydrochlorothiazide after an oral dose is rapid (T_{max} about 2 hours), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60-80% after oral administration.

The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated administration, and accumulation is minimal when administered once daily.

The distribution and elimination kinetics have generally been described by a bi-exponential decay function, with a terminal half-life of 6-15 hours. Greater than 95% of the absorbed dose is excreted as unchanged compound in the urine.

Amlodipine/valsartan/hydrochlorothiazide

Following oral administration of Exforge HCT in normal healthy adults, peak plasma concentrations of amlodipine, valsartan and hydrochlorothiazide are reached in 6-8 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of amlodipine, valsartan and hydrochlorothiazide from Exforge HCT are the same as when administered as individual dosage forms. The bioavailability of amlodipine, valsartan, and hydrochlorothiazide were not altered when Exforge HCT was administered with food.

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

Pharmacokinetics in the elderly: Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in AUC and elimination half-life.

Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly compared to younger patients.

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Since the three components are equally well tolerated in younger and elderly patients, no dosage adjustment of Exforge HCT is necessary in elderly patients.

Pharmacokinetics in patients with impaired renal function:

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment.

As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, there is no apparent correlation between renal function (measured by creatinine clearance) and systemic exposure to valsartan (measured by AUC) in patients with different degrees of renal failure. A trial in 5 normotensive patients undergoing haemodialysis

demonstrated that complete loss of renal function does not lead to a gross increase in the exposure to valsartan and does not have a major impact on the kinetics of valsartan. This study also confirmed that valsartan is not removed from the plasma by haemodialysis.

Renal clearance of hydrochlorothiazide is composed of passive filtration and active secretion into the renal tubule. As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide (see "CONTRAINDICATIONS" and "PRECAUTIONS").

Pharmacokinetics in patients with impaired hepatic function: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60% in AUC. In a small number of patients with mild to moderate hepatic impairment given single doses of 5 mg, amlodipine half-life has been prolonged. Worsening of liver function test values may occur.

About 70% of the absorbed valsartan dose is excreted in the bile, mainly as unchanged compound. The AUC with valsartan has been observed to approximately double in patients with mild or moderate hepatic impairment including patients with biliary obstructive disorders (see "PRECAUTIONS - Impaired hepatic function"). There are no data available on the use of valsartan in patients with severe hepatic dysfunction (see "CONTRAINDICATIONS").

Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.

Care should be exercised in patients with liver disease (see "PRECAUTIONS").

CLINICAL TRIALS

There have been no long-term, clinical outcome studies using these fixed-dose combination tablets.

Exforge HCT was studied in an 8-week double-blind, active controlled study in patients with moderate to severe essential hypertension (mean sitting diastolic blood pressure ≥100 mmHg and <120 mmHg and mean sitting systolic blood pressure ≥145 mmHg and <200 mmHg). Patients with renal or hepatic impairment, type 1 diabetes and uncontrolled type 2 diabetes, and cardiovascular conditions including heart failure requiring treatment, history of myocardial infarction, angina, revascularisation procedure, moderate or malignant retinopathy, hypertensive encephalopathy, cerebrovascular accident or transient ischemic attack were excluded from the study. A total of 2,271 patients with moderate to severe hypertension (mean baseline systolic/diastolic blood pressure was 170/107 mmHg) received treatments of amlodipine/valsartan/hydrochlorothiazide 10/320/25 mg, valsartan/hydrochlorothiazide 320/25 mg, amlodipine/valsartan 10/320 mg, or hydrochlorothiazide/amlodipine 25/10 mg. At study initiation patients were assigned lower doses of their treatment combination and were titrated to their full treatment dose by week 2. A total of 55% of patients were male, 14% were 65 years or older, 72% were Caucasian and 17% were Black.

At week 8, the mean reductions in systolic/diastolic blood pressure were 39.7/24.7 mmHg with Exforge HCT (n=571), 32.0/19.7 mmHg with valsartan/hydrochlorothiazide (n=553), 33.5/21.5 mmHg with amlodipine/valsartan (n=558) and 31.5/19.5 with amlodipine/hydrochlorothiazide (n=554). The triple combination therapy was statistically superior to each of the three dual combination treatments in reduction of diastolic and systolic blood pressures. The reductions in systolic/diastolic blood pressure with Exforge HCT were 7.6/5.0 mmHg greater than with valsartan/hydrochlorothiazide, 6.2/3.3 mmHg greater than with amlodipine/valsartan, and

8.2/5.3 mmHg greater than with amlodipine/hydrochlorothiazide (see Figure 1). The full blood pressure lowering effect was achieved 2 weeks after being on their maximal dose of Exforge HCT (See Figure 2 and 3). Statistically significant greater proportions of patients achieved BP control (<140/90 mmHg) with Exforge HCT (71%) compared to each of the three dual combination therapies (45-54%).

Figure 1: Reduction in Mean Blood Pressure at Endpoint

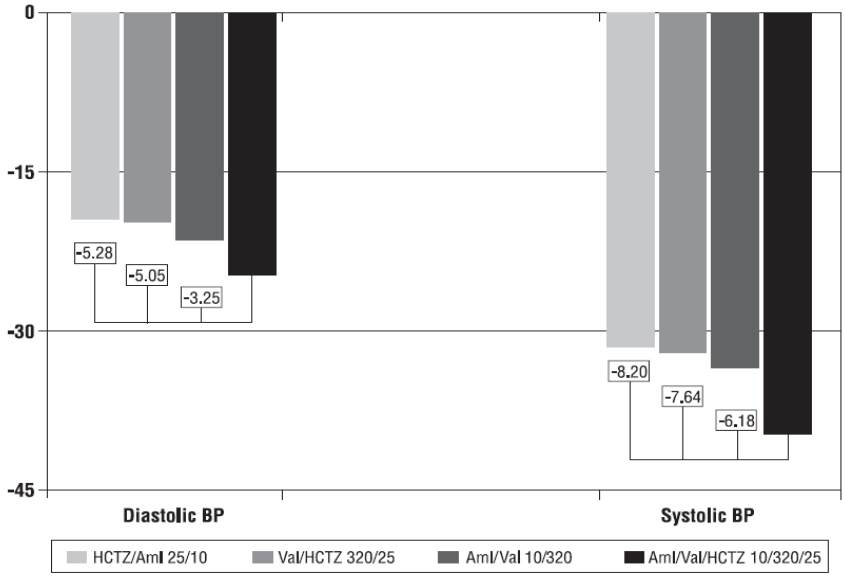


Figure 2: Mean Sitting Diastolic Blood Pressure by Treatment and Week

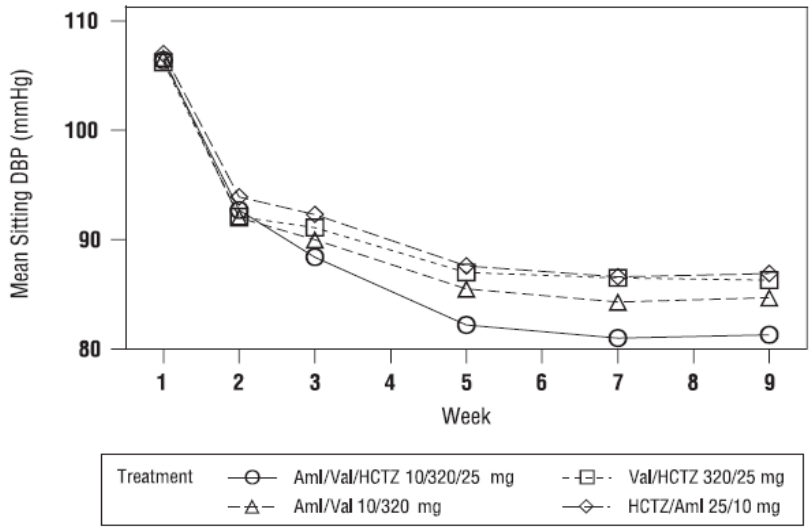
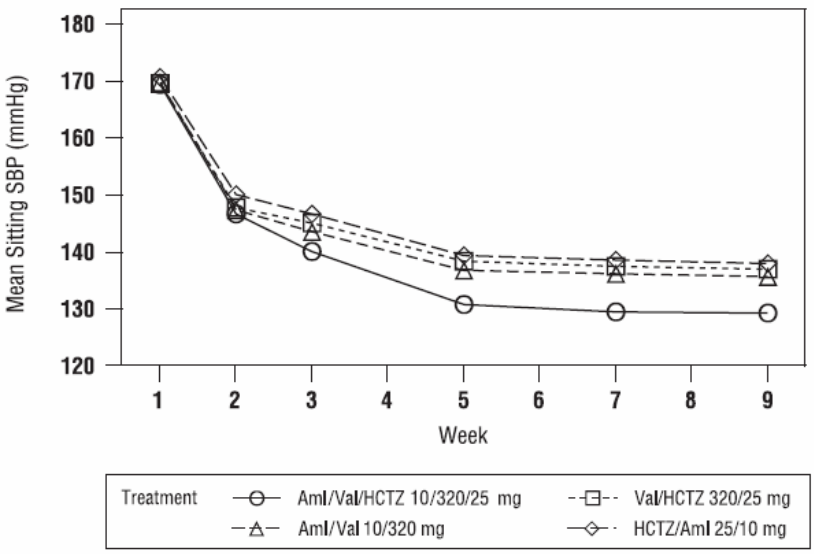


Figure 3: Mean Sitting Systolic Blood Pressure by Treatment and Week



A subgroup of 268 patients was studied with ambulatory blood pressure monitoring. Clinically and statistically superior reductions in 24-hour systolic and diastolic blood pressures with the triple combination compared to valsartan/hydrochlorothiazide, amlodipine/valsartan, and hydrochlorothiazide/amlodipine were observed.

Age, gender, and race did not significantly influence the response to Exforge HCT.

Similar studies have not been carried out with the lower dose strength Exforge HCT combinations.

The beneficial affects on mortality and cardiovascular morbidity are unknown.

Withdrawal and rebound effects on efficacy have not been studied.

There have been not sufficient studies carried out to support the use of this product in the context of add-on or step-up dose titration from the dual combinations (see "DOSAGE AND ADMINISTRATION").

INDICATIONS

Exforge HCT is indicated ONLY as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of amlodipine, valsartan and hydrochlorothiazide taken either as three single component formulations or as dual –component formulation with a single-component formulation, all components at the same dose level. Treatment should not be initiated with these fixed-dose combinations (see "DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

- Hypersensitivity to the active substances, dihydropyridine derivatives, other sulfonamide-derived drugs, or to any of the excipients
- Severe hepatic impairment; biliary cirrhosis and cholestasis
- Severe renal impairment (GFR<30 ml/min/1.73 m2), anuria and patients undergoing dialysis
- Refractory hypokalaemia, hyponatremia, hypercalcemia and symptomatic hyperuricemia
- Pregnancy

PRECAUTIONS

Hypotension, Sodium and/or Volume depleted patients: Excessive hypotension, including orthostatic hypotension was seen in 1.7% of patients treated with the maximum dose of Exforge HCT (10/320/25 mg) compared to 1.8% of valsartan/hydrochlorothiazide (320/25 mg) patients, 0.4% of amlodipine/valsartan (10/320 mg) patients, and 0.2% of hydrochlorothiazide/amlodipine (25/10 mg) patients in a controlled trial in patients with moderate to severe uncomplicated hypertension. In patients with an activated renin-angiotensin system, such as volume-and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving angiotensin receptor blockers. This condition should be corrected prior to administration of Exforge HCT, or the treatment should start under close medical supervision.

If excessive hypotension occurs with Exforge HCT, the patient should be placed in the supine position and, if necessary, given an i.v. infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

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

Renal artery stenosis: There has been no long-term use of Exforge HCT in patients with unilateral or bilateral renal artery stenosis. Short-term administration of valsartan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, since other drugs that affect the renin-angiotensin-aldosterone system (RAAS) may increase blood urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis, monitoring of both parameters is recommended as a safety measure.

Kidney transplantation: To date there is no experience of the safe use of Exforge HCT in patients who have had a recent kidney transplantation.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Serum electrolyte changes:

Amlodipine/valsartan/hydrochlorothiazide

In the controlled trial of Exforge HCT, the opposite effects of valsartan 320 mg and hydrochlorothiazide 25 mg on serum potassium approximately balanced each other in many

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

In the controlled trial of Exforge HCT in moderate to severe hypertensive patients, the incidence of hypokalemia (serum potassium <3.5 mEq/L) at any time post-baseline with the maximum dose of Exforge HCT (10/320/25 mg) was 9.9% compared to 24.5% with hydrochlorothiazide/amlodipine (25/10 mg), 6.6% with valsartan/hydrochlorothiazide (320/25 mg), and 2.7% with amlodipine/valsartan (10/320 mg). One patient (0.2%) discontinued therapy due to an adverse event of hypokalemia in each of the Exforge HCT and hydrochlorothiazide/amlodipine groups. The incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4% with Exforge HCT compared to 0.2-0.7% with the dual therapies

Valsartan

Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) could lead to hyperkalaemia and should be used with caution.

Hydrochlorothiazide

Hypokalaemia has been reported under treatment with thiazide diuretics including hydrochlorothiazide. Frequent monitoring of potassium is recommended.

Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatremia and hypochloroaemic alkalosis. Thiazides, including hydrochlorothiazide increase the urinary excretion of magnesium, which may result in hypomagnesaemia. As for any patient receiving diuretic therapy, periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals.

Use in patients with heart failure/Post-myocardial infarction: In general, calcium channel blockers should be used with caution in patients with heart failure. As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan. Use of valsartan in patients with heart failure or post-myocardial infarction commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed. Patients with more complicated post-myocardial infarction courses may be at increased risk for hypotension and/or renal dysfunction. Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction. An assessment of renal function should always be conducted in patients with heart failure or post-myocardial infarction.

An increase in the mortality rate among patients who received a combination of valsartan, ACE inhibitors and beta blockers has been observed in clinical trials. Concurrent administration of ACE inhibitors, beta blockers and valsartan is not recommended.

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

Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of Exforge HCT 10/320/25 mg, since available data in these patient populations is limited (see "PRECAUTIONS - Increased angina").

Systemic lupus erythematosus: Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances: Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides, and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required.

Hyperuricaemia may occur or gout may be precipitated incertain patients receiving thiazide therapy. Thiazides may reduce urinary calcium excretion and cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Hepatic injury: Cases of clinically significant liver disease have occurred with some angiotensin II receptor antagonists. Hepatitis has been reported rarely with valsartan.

Use in patients with hepatic impairment: Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolized by the liver. In patients with mild to moderate hepatic impairment without cholestasis, Exforge HCT, the maximum recommended dose is 80 mg valsartan, and therefore, Exforge HCT is not suitable in this group of patients. Patients with severe hepatic impairment, biliary cirrhosis or cholestasis should not take Exforge HCT (see "CONTRAINDICATIONS").

Use in patients with renal impairment: No dosage adjustment of Exforge HCT is required for patients with mild to moderate renal impairment. Monitoring of creatinine and potassium levels is advised for patients with moderate renal impairment. Patients with severe renal impairment should not take Exforge HCT (see "CONTRAINDICATIONS").

Primary hyperaldosteronism: Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan Exforge as their renin-angiotensin system is affected by the primary disease. Therefore, Exforge HCT is not recommended in this population.

Photosensitivity: Cases of photosensitivity reactions have been reported with thiazide diuretics. If photosensitivity reaction occurs during treatment with Exforge HCT, it is recommended to stop the treatment. If a readministration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

General: Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Elderly (age 65 years or over): Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of Exforge HCT 10/320/25 mg, since available data in this patient population are limited.

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

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

Carcinogenicity:

No carcinogenicity studies have been conducted with the amlodipine, valsartan and hydrochlorothiazide combination. However, amlodipine, valsartan and hydrochlorothiazide have been tested individually for carcinogenicity with generally negative results.

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

Valsartan: In animal studies, there was no clear evidence of carcinogenic activity when valsartan was administered in the diet to male and female mice at doses up to 160 mg/kg/day for two years, but systemic exposure (plasma AUC value) at this dose level was lower than that achieved in humans. There was no clear evidence of carcinogenic activity in male or female rats at up to 200 mg/kg/day with plasma concentrations approximately 1.5 times the concentrations achieved in humans (based on AUC) at the maximum recommended dose (160 mg bid).

Hydrochlorothiazide: Two-year feeding studies in mice and rats showed no evidence of carcinogenic potential in female mice at doses up to approximately 600 mg/kg/day, or in male and female rats at doses up to approximately 100 mg/kg/day. However, there was equivocal evidence for hepatocarcinogenicity in male mice treated with hydrochlorothiazide alone at approximately 600 mg/kg/day.

Genotoxicity

No genotoxicity studies have been conducted with the amlodipine, valsartan and hydrochlorothiazide combination. However, amlodipine, valsartan and hydrochlorothiazide have been tested individually for genotoxicity with generally negative results.

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

Valsartan: Genotoxicity studies showed that valsartan does not cause gene mutation in bacterial or mammalian cells, nor does it induce chromosomal damage *in vitro* or *in vivo*.

Hydrochlorothiazide: Hydrochlorothiazide did not induce gene mutation in bacteria or chromosome damage in mammalian cells in several *in vitro* and *in vivo* assays. However positive results were obtained in a mammalian cell assay for gene mutation (mouse lymphoma cell assay) and in two other tests (sister chromatid exchange assay in Chinese hamster ovary cells and nondisjunction assay in *Aspergillus nidulans*).

Effects on fertility

No specific fertility studies were conducted with the amlodipine/valsartan/hydrochlorothiazide combination;

Testes, ovaries and secondary sex organs were evaluated in other toxicity studies with the amlodipine/valsartan (Exforge) combination. The primary and secondary sex organs were not affected in these toxicity studies, in which rats and marmosets were treated with this combination for up to 13 weeks.

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

Valsartan: Fertility of male and female rats was not affected at oral doses up to 200 mg/kg/day, with systemic exposure similar to that in human patients at the maximum recommended dose.

Hydrochlorothiazide: The effects of valsartan and hydrochlorothiazide in combination and hydrochlorothiazide alone on fertility have not been investigated.

Use in Pregnancy (Category D)

Exforge HCT must not be used during pregnancy (see "CONTRAINDICATIONS") or in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, Exforge HCT must be discontinued as soon as possible.

Drugs that act on the renin-angiotensin-aldosterone system (RAAS) can cause foetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors (a specific class of drugs acting on the RAAS).

Due to the mechanism of action of angiotensin II antagonists, a risk to the foetus cannot be excluded. The use of drugs that act directly on the renin-angiotensin-aldosterone system (RAAS) during the second and third trimesters of pregnancy has been associated with foetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have inadvertently taken valsartan. Pregnant women who are taking angiotensin II receptor antagonists (ARAs) should be changed as quickly as possibly to other antihypertensive medication to maintain normal blood pressure. It is generally advisable not to use ARAs for the management of hypertension in women who are likely to become pregnant.

Calcium channel blockers carry the potential to produce foetal hypoxia associated with maternal hypotension. Accordingly they should not be used in pregnant women unless the potential benefit outweighs the risk to the foetus.

No reproductive toxicity studies have been conducted with amlodipine, valsartan and hydrochlorothiazide combination. There was no evidence of teratogenicity in rats dosed with the amlodipine/valsartan combinations during organogenesis at doses up to 20:320 mg/kg/day PO. Foetotoxicity was observed in association with maternal toxicity (≥10:160 mg/kg/day) in rats at amlodipine/valsartan doses of 20:320 mg/kg/day and included decreased foetal weights, dilated ureters and delayed/incomplete ossification. The (AUC) exposures at these doses were 3-10x the expected human exposure to amlodipine/valsartan at the maximum proposed clinical dose (10:160mg/day).

Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with foetal or neonatal thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults.

There was no evidence of teratogenicity in mice, rats and rabbits dose with the valsartan/hydrochlorothiazide combination during organogenesis at up to 600/187.5, 200/62.5 and 10/3.125 mg/kg/day PO, respectively. Foetotoxicity was observed in association with maternal toxicity in rats and rabbits at valsartan/hydrochlorothiazide doses of 200/62.5 mg/kg/day and 10/3.125 mg/kg/day. Decreased foetal weights, absent renal papillae and delayed ossification were observed in rats and increased late resorptions in rabbits.

Use in Lactation

It is not known whether amlodipine and/or valsartan are excreted in human milk. Valsartan was excreted in the milk of lacting rats. Hydrochlorothiazide crosses the placenta and is excreted in human milk. It is therefore not advisable for women who are breast-feeding to use Exforge HCT.

Interactions with Other Drugs

No formal interaction studies with other medicinal products were performed with Exforge HCT. Thus, only information on interactions with other medicinal products that are known for the individual active substances is provided in this section.

However, it is important to take into account that Exforge HCT may increase the antihypertensive effect of other antihypertensive agents (e.g. alpha blockers, other diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia).

Concomitant use not recommended

Exforge HCT individual component	Known interactions with the following agents	Effect of the interaction with other medicinal products
Valsartan and HCT	*Lithium*	Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and Thiazides. Despite the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.
Valsartan	*Medicinal products affecting Potassium*	Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) requires caution and frequent monitoring of potassium levels.

Caution required with concomitant use

Exforge HCT individual component	Known interactions with the following agents	Effect of the interaction with other medicinal products
Amlodipine	*CYP3A4 inhibitors*	A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50% and the effect of amlodipine is increased). The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded.
	CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum).	Co-administration may lead to reduced plasma concentrations of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal. In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin (glyceryl trinitrate), digoxin, warfarin, atorvastatin, aluminium/magnesium antacid, cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, ethanol and oral hypoglycaemic drugs.
Valsartan and HCT	*Corticosteroids, ACTH*	Electrolyte depletion, particularly hypokalaemia, may be increased.
	Medicinal products affecting Potassium	See "Concomitant use not recommended - Valsartan - *Medicinal products affecting Potassium*"
	Medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics)	Periodic monitoring of serum potassium and ECG is recommended when Exforge HCT is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the torsades de pointes inducing medicinal products (which include some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes. • Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide) • Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide) • Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, suitopride, amisulpride, tiapride, pimozide, haloperidol, droperidol, methadone) • Others (e.g. bepridil, cisapride, diphemanil, erythromycin i.v., halofantrin, ketanserin, mizolastin, pentamidine, moxifloxacine,

		terfenadine, vincamine i.v.) Periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals to detect possible electrolyte imbalance, especially in patients with other risk factors such as impaired renal function, treatment with other medicinal products or history of prior electrolyte imbalances. See "PRECAUTIONS - Serum electrolyte changes"
	Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3g/day), and non-selective NSAIDs	NSAIDS can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Exforge HCT and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination as well as adequate hydration of the patients. Caution is particularly recommended in elderly patients or those with pre-existing renal impairment (See "Caution required with concomitant use - HCT - *Non-steroidal anti-inflammatory drugs).*
HCT	*Alcohol, anesthetics and sedatives*	Potentiation of orthostatic hypotension may occur.
	Amantadine	Thiazides, including hydrochlorothiazide may increase the risk of adverse reactions caused by Amantadine.
	Anticholinergic agents (e.g. atropine, biperiden)	The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.
	Antidiabetic agents(e.g. insulin and oral antidiabetic agents) *- Metformin*	Thiazide diuretics, including hydrochlorothiazide, may increase blood glucose. It may prove necessary to readjust the dosage of insulin and of oral antidiabetic agents. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.
	Beta blockers and diazoxide	Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide may enhance the hyperglycaemic effect of diazoxide.

Carbamazepine	Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatremia. Such patients should therefore be advised about the possibility of hyponatremic reactions, and should be monitored accordingly.
Cholestyramine and cholestipol resins	Single doses of cholestyramine or colestipol resins reduced the absorption of hydrochlorothiazide by up to 85 and 43 percent respectively.
Cyclosporin	Concomitant treatment with cyclosporin may increase the risk of hyperuricemia and gout-type complications.
Cytotoxic agents (e.g. cyclophosphamide, methotrexate)	Co-administration of thiazide diuretics, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.
Digitalis glycosides	Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects, favouring the onset of digitalis-induced cardiac arrhythmias.
Iodine contrasting agents	In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be re-hydrated before the administration.
Medicinal product affecting Potassium (kaliuretic diuretics, amphotericin, carbenoxolone, penicillin G, salicylic acid derivative)	The hypokalemic effect of diuretics may be increased by kaliuretic diuretics, amphotericin, carbenoxolone, penicillin G, and salicylic acid derivatives. If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see "PRECAUTIONS, Serum electrolyte changes").
Medicinal products used in the treatments for gout (probenecid, sulfinpyrazone and allopurinol)	Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol. Thiazides may also increase serum uric acid levels, and the dose of uricosuric agents such as probenecid or sulfinpyrazone may need to be increased.
Methyldopa	There have been reports in the literature of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.
Non-depolarising skeletal muscle relaxants (e.g. tubocurarine)	Thiazides, including hydrochlorothiazide, potentiate the action of non-depolarising muscle relaxants (e.g. curare derivatives).
Non-steroidal anti-inflammatory drugs	Concomitant administration of NSAIDs (e.g. salicylic acid derivatives, indomethacin) may weaken the diuretic and antihypertensive activity of the thiazide component of Exforge HCT. Concurrent hypovolemia may induce

	acute renal failure.
Other diuretics and antihypertensive agents	The antihypertensive effect may be increased with concomitant use of other antihypertensive drugs. The thiazide component of Co-Diovan may enhance the hyperglycaemic effect of beta-blockers and diazoxide.
Pressor amines(e.g. noradrenalin, adrenaline)	The effect of pressor amines may be decreased.
Tetracyclines	Concomitant administration of tetracyclines and thiazide diuretics increases the risk for tetracycline induced increase in urea. This interaction is probably not applicable to doxycycline.
Vitamin D and Calcium salts	Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

No interactions

Exforge HCT individual component	**Known interactions with the following agents**	**Effect of the interaction with other medicinal products**
Valsartan	*Highly protein-bound, such as diclofenac, frusemide and warfarin*	As valsartan is not metabolised to a significant extent, clinically relevant drug-drug interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are not expected with valsartan. Although valsartan is highly bound to plasma proteins, in vitro studies have not shown any interaction at this level with a range of molecules which are also highly protein-bound, such as diclofenac, frusemide and warfarin. Some of these substances could interact with the hydrochlorothiazide component of Exforge HCT (See "Caution required with concomitant use – HCT").
	Others (cimetidine, warfarin, frusemide, digoxin, atenolol, indomethacin hydrochlorothiazide, amlodipine, glibenclamide)	In monotherapy with valsartan, no drug interactions of clinical significance have been found with the following drugs: cimetidine, warfarin, frusemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. Some of these substances could interact with the hydrochlorothiazide component of Exforge HCT (See "Caution required with concomitant use – HCT").

Amlodipine	*Grapefruit juice*	Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers. In a study in 20 healthy volunteers, co administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg had no significant effect on the pharmacokinetics of amlodipine.
	Sildenafil	A single 100 mg dose of sildenafil in 16 patients with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.
	Cyclosporin.	The pharmacokinetics of cyclosporin were not altered when cyclosporin was coadministered with amlodipine in renal transplant patients. The patients were not taking corticosteroids. (See "Caution required with concomitant use – HCT – *Cyclosporin*")

ADVERSE EFFECTS

The Safety of Exforge HCT is based on that of Exforge HCT, Exforge (amlodipine/valsartan), and the individual components.

Adverse reactions with suspected relationship to Exforge HCT:

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

In the controlled trial of Exforge HCT, where only the maximum dose (10/320/25 mg) was evaluated, safety data was obtained in 582 patients with hypertension. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

The overall frequency of adverse reactions was not related to gender, age, or race. In the active controlled clinical trial, discontinuation due to side effects occurred in 4.0% of patients treated with Exforge HCT 10/320/25 mg compared to 2.9% of patients treated with valsartan/hydrochlorothiazide 320/25 mg, 1.6% of patients treated with amlodipine/valsartan 10/320 mg, and 3.4% of patients treated with hydrochlorothiazide/amlodipine 25/10 mg. The most common reasons for discontinuation of therapy with Exforge HCT were dizziness (1.0%) and hypotension (0.7%).

The adverse reactions that occurred in the active controlled clinical trial in at least 2% of patients treated with Exforge HCT but at a higher incidence in the triple combination group than in any one of the dual combinations groups are presented in the table below:

Table 1

Preferred term	Aml/Val/HCT 10/320/25 mg N=582 n (%)	Val/HCT 320/25 mg N=559 n (%)	Aml/Val 10/320 mg N=566 n (%)	HCT/Aml 25/10 mg N=561 n (%)
Dizziness	45 (7.7)	39 (7.0)	13 (2.3)	22 (3.9)
Edema peripheral	26 (4.5)	5 (0.9)	48 (8.5)	50 (8.9)
Dyspepsia	13 (2.2)	5 (0.9)	6 (1.1)	2 (0.4)
Fatigue	13 (2.2)	15 (2.7)	12 (2.1)	8 (1.4)
Muscle spasms	13 (2.2)	7 (1.3)	7 (1.2)	5 (0.9)
Back pain	12 (2.1)	13 (2.3)	5 (0.9)	12 (2.1)
Nausea	12 (2.1)	7 (1.3)	10 (1.8)	12 (2.1)

Adverse reactions with suspected relationship to Exforge:

The safety of Exforge has been evaluated in five controlled clinical studies with 5,175 patients, 2,613 of whom received amlodipine in combination with valsartan.

Adverse drug reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 2

Infections and infestations	
Common:	Nasopharyngitis, influenza
Immune system disorders	
Rare:	Hypersensitivity
Eye disorders	
Rare	Visual disturbance
Psychiatric disorders	
Rare:	Anxiety
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, somnolence, dizziness postural, paraesthesia
Ear and labyrinth disorders	
Uncommon:	Vertigo
Rare:	Tinnitus
Cardiac disorders	
Uncommon:	Tachycardia, palpitations
Rare:	Syncope
Vascular disorders	
Uncommon:	Orthostatic hypotension
Rare:	Hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Cough, pharyngolaryngeal pain
Gastrointestinal disorders	
Uncommon:	Diarrhoea, nausea, abdominal pain, constipation, dry mouth
Skin and subcutaneous tissue disorders	
Uncommon:	Rash, erythema
Rare:	Hyperhidrosis, exanthema, pruritus
Musculoskeletal and connective tissue disorders	
Uncommon:	Joint swelling, back pain, arthralgia
Rare:	Muscle spasm, sensation of heaviness
Renal and urinary disorders	
Rare:	Pollakiuria, polyuria
Reproductive system and breast disorders	
Rare:	Erectile dysfunction
General disorders and administration site conditions	
Common:	oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia, hot flush

Additional information on individual components

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

Amlodipine

Other additional adverse experiences reported in clinical trials and post marketing reports with amlodipine monotherapy, irrespective of their causal association with the study drug, were as follows:

The most commonly observed adverse event was vomiting.

Less commonly observed adverse events were peripheral ischaemia, alopecia, anorexia, altered bowel habits, dyspepsia, dysphagia, flatulence, dyspnoea, epistaxis, rhinitis, gastritis, gingival hyperplasia, gynaecomastia, hyperglycaemia, impotence, increased urinary frequency, malaise, sexual dysfunction, insomnia, nervousness, depression, abnormal dreams, depersonalisation, mood changes, pain, rigors, weight gain, arthrosis, muscle cramps, myalgia, hypoesthesia, tremor, peripheral neuropathy, pancreatitis, leucopenia, thrombocytopenia, purpura vasculitis, conjunctivitis, diplopia, eye pain, micturition frequency and disorder, nocturia, sweating increased, thirst, angioedema and erythema multiforme.

Rarely observed adverse events were cardiac failure, pulse irregularity, extrasystoles, skin discolouration, urticaria, skin dryness, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, increased appetite, loose stools, coughing, dysuria, parosmia, taste perversion, xerophthalmia and weight decrease.

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

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

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

Valsartan (Diovan)

Other additional adverse experiences reported in clinical trials and post marketing reports with valsartan monotherapy in the hypertension indication, irrespective of their causal association with the study drug, were as follows:

Viral infections, upper respiratory infections, pharyngitis, sinusitis, rhinitis, neutropenia, thrombocytopenia, insomnia, libido decrease, myalgia, dyspepsia, flatulence, muscle cramps chest pain, anorexia, vomiting, dyspnoea, elevated liver enzymes and very rare reports of hepatitis. Altered renal function, especially in patients treated with diuretics or in patients with renal impairment, acute renal failure, renal insufficiency, angioedema and hypersensitivity (vasculitis, serum sickness) can occur.

In rare cases, valsartan may be associated with decreases in haemoglobin and haematocrit. In controlled clinical trials, 0.8% and 0.4% of patients receiving valsartan showed significant

decreases (>20%) in haematocrit and haemoglobin, respectively. In comparison, 0.1% of patients receiving placebo showed significant decreases in both haematocrit and haemoglobin.

Neutropenia was observed in 1.9% of patients treated with valsartan versus 1.6% of patients treated with an ACE inhibitor.

In heart failure patients, greater than 50% increases in creatinine were observed in 3.9% of valsartan-treated patients compared to 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients.

In heart failure patients, greater than 20% increases in serum potassium were observed in 10% of valsartan-treated patients compared to 5.1% of placebo-treated patients.

In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

Valsartan/hydrochlorothiazide (Co-Diovan)

Other additional adverse experiences reported with valsartan/hydrochlorothiazide combination therapy were as follows: Upper respiratory tract infection, abdominal pain upper, arthritis, bronchitis, bronchitis acute, chest pain, dyspnoea, gastroenteritis, hypoesthesia, hypokalaemia, insomnia, muscle strain, nasal congestion, neck pain, otitis media, pain in the extremity, pyrexia, sinus congestion, sinusitis, ligament sprain, urinary tract infection, viral infection, vision blurred, angioedema, serum sickness, vasculitis, renal impairment, myalgia, decrease in serum potassium, elevation in creatinine and blood urea nitrogen. There have also been reported several cases of hydrochlorothiazide-induced pulmonary oedema with granulocytic infiltration and IgG deposition in alveolar membranes. Non-cardiogenic pulmonary oedema may be an immunologically mediated rare idiosyncratic reaction to hydrochlorothiazide.]

Hydrochlorothiazide

Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Exforge HCT. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Common: Urticaria and other forms of rash, loss of appetite, mild nausea and vomiting, postural hypotension, which may be aggravated by alcohol, anaesthetics or sedatives, and impotence. Electrolyte and metabolic disorders (see “PRECAUTIONS”).

Rare: Photosensitisation, abdominal distress, constipation, diarrhoea, and gastrointestinal discomfort, intrahepatic cholestasis or jaundice, cardiac arrhythmias, headache, dizziness or light-headedness, sleep disturbances, depression, paraesthesia, disturbances of vision, and thrombocytopenia, sometimes with purpura.

Very rare: Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, pancreatitis, leukopenia, agranulocytosis, bone marrow depression, haemolytic anaemia, hypersensitivity reactions, respiratory distress including pneumonitis and pulmonary oedema.

Laboratory findings:

Clinical laboratory test findings were obtained in a controlled trial of Exforge HCT administered at the maximal dose of 10/320/25 mg compared to maximal doses of dual therapies, i.e. valsartan/hydrochlorothiazide 320/25 mg, amlodipine/valsartan 10/320 mg, and hydrochlorothiazide/amlodipine 25/10 mg.

Creatinine

In hypertensive patients, greater than 50% increases in creatinine occurred in 2.1% of Exforge HCT patients compared to 2.4% of valsartan/hydrochlorothiazide patients, 0.7% of amlodipine/valsartan patients, and 1.8% of hydrochlorothiazide/amlodipine patients.

In heart failure patients, greater than 50% increases in creatinine were observed in 3.9% of valsartan-treated patients compared to 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients.

Blood Urea Nitrogen

In hypertensive patients, greater than 50% increases in blood urea nitrogen were observed in 29.5% of Exforge HCT-treated patients compared to 29.3% of valsartan/hydrochlorothiazide patients, 15.8% of amlodipine/valsartan patients, and 18.5% of hydrochlorothiazide/amlodipine patients. The majority of blood urea nitrogen values remained within normal limits.

In heart failure patients, greater than 50% increases in blood urea nitrogen were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

Liver Function Tests

Occasional elevations (greater than 150%) of liver chemistries occurred in Exforge HCT-treated patients.

Serum Potassium

In hypertensive patients, greater than 20% decreases in serum potassium were observed in 6.5% of Exforge HCT-treated patients compared to 3.3% of valsartan/hydrochlorothiazide patients, 0.4% of amlodipine/valsartan patients, and 19.3% of hydrochlorothiazide/amlodipine patients. Greater than 20% increases in potassium were observed in 3.5% of Exforge HCT-treated patients compared to 2.4% of valsartan/hydrochlorothiazide patients, 6.2% of amlodipine/valsartan patients, and 2.2% of hydrochlorothiazide/amlodipine patients.

In heart failure patients, greater than 20% increases in serum potassium were observed in 10% of valsartan-treated patients compared to 5.1% of placebo-treated patients.

DOSAGE AND ADMINISTRATION

Exforge HCT is ONLY indicated as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of amlodipine, valsartan and hydrochlorothiazide taken either as three single component

formulations or as dual –component formulation with a single-component formulation, all components at the same dose level.

Therefore, if blood pressure is not controlled on one of the three possible dual combination therapies, then any third monotherapy must be first added as an individual therapy until dose titration is complete and BP control established before the triple fixed-dose combination may be introduced.

Similarily, there can be no direct dose-titration within the Exforge HCT product range. If a patient's blood pressure is uncontrolled at one of the lower dosage of the combination, dose titration must be carried out with the separately administered components.

Children and adolescents: Exforge HCT is not recommended for use in patients aged below 18 years due to a lack of safety and efficacy data.

Patients with renal impairment: Exforge HCT is contraindicated in severe renal impairment (creatinine clearance < 30mL/min) (see "CONTRAINDICATIONS"). No dosage adjustment is required for patients with mild to moderate renal impairment (see "PRECAUTIONS"). Monitoring of creatinine and potassium levels is advised for patients with moderate renal impairment.

Patients with hepatic impairment: Exforge HCT is contraindicated in severe hepatic impairment, biliary cirrhosis or cholestasis and in patients undergoing dialysis (see "CONTRAINDICATIONS"). In patients with mild to moderate hepatic impairment without cholestasis the maximum recommended dose is 80 mg valsartan, and therefore, Exforge HCT is not suitable in this group of patients (see "PRECAUTIONS").

Heart failure and coronary artery disease: There is limited experience with the use of Exforge HCT, particularly at the maximum dose, in patients with heart failure and coronary artery disease. Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of Exforge HCT 10/320/25.

Elderly (age 65years or over): Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of Exforge HCT 10/320/25, since available data in this patient population are limited.

Administration: The recommended dose is one tablet per day. Exforge HCT can be taken with or without food. It is recommended to take Exforge HCT with some water.

OVERDOSAGE

Symptoms: There is no experience of overdose with Exforge HCT. Overdose with valsartan may result in pronounced hypotension with dizziness which could lead to depressed level of consciousness, circulatory collapse and/or shock. Overdose with amlodipine may result in excessive peripheral vasodilation with marked hypotension and possibly reflex tachycardia. Dysrhythmias may occur following overdose with any calcium antagonists. Hypotension and bradycardia are usually seen within one to five hours following overdose. Hypotension can persist for longer than 24 hours despite treatment. Cardiac rhythm disturbances have been noted to persist for up to seven days. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment: Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to Exforge HCT overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both valsartan and amlodipine are unlikely to be removed by haemodialysis whereas clearance of hydrochlorothiazide will be achieved by dialysis.

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

PRESENTATION AND STORAGE CONDITIONS

Exforge HCT 5/160/12.5® (5mg amlodipine, 160mg valsartan and 12.5mg hydrochlorothiazide): white, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with "NVR" on one side and "VCL" on the other. Blister packs of 7, 14, 28, 30 and 56.

Exforge HCT 10/160/12.5® (10mg amlodipine, 160mg valsartan and 12.5mg hydrochlorothiazide): pale yellow, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with "NVR" on one side and "VDL" on the other. Blister packs of 7, 14, 28, 30 and 56.

Exforge HCT 5/160/25® (5mg amlodipine 160mg valsartan and 25mg hydrochlorothiazide): yellow, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with "NVR" on one side and "VEL" on the other. Blister packs of 7, 14, 28, 30 and 56.

Exforge HCT 10/160/25® (10mg amlodipine, 160mg valsartan and 25mg hydrochlorothiazide): brown-yellow, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with "NVR" on one side and "VHL" on the other. Blister packs of 7, 14, 28, 30 and 56.

Exforge HCT 10/320/25® (5mg amlodipine, 320mg valsartan and 25mg hydrochlorothiazide): brown-yellow, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with "NVR" on one side and "VFL" on the other. Blister packs of 7, 14, 28, 30 and 56.

Not all pack sizes may be marketed.

Storage: Store below 30 degrees Celsius. Protect from moisture.

SPONSOR

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® = Registered Trademark

POISON SCHEDULE

Exforge HCT is a Schedule 4 medicine.

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration: 1 April 2010

PER dated September 2009, S31 Response PM-2008-03499-3-3-pce-2, CER dated 1 December 2009, the Delegate's Overview (DO) dated 21 December 2009 and Pre-ADEC response dated 8 January 2010 and Post-ADEC PI negotiations dated 4 March 2010.