Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Amlodipine/Valsartan

Proprietary Product Name: Exforge/Ejocia 5/320; Exforge Ejocia 10/320

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

October 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Major Variation (New Strength)
Decision:	Approved
Date of Decision:	26 July 2010
Active ingredient(s):	Amlodipine (as besylate) and valsartan
Product Name(s):	Exforge /Ejocia 5/320
	Exforge /Ejocia 10/320
Sponsor's Name and Address:	Novartis Pharmaceuticals Australia Pty Ltd, PO Box 101, North Ryde, NSW 1670
Dose form(s):	tablets – film-coated
Strength(s):	5 or 10 mg of amlodipine and 320 mg of valsartan
Container(s):	PA/Al/PVC\\Al Blisters
Pack size(s):	Packs of 7, 14, 28, 30 and 56
Approved Therapeutic use:	Exforge is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed dose combination.
Route(s) of administration:	Oral (PO)
Dosage:	For convenience, patients adequately controlled on valsartan and amlodipine may be switched to Exforge/Ejocia containing the same component doses from separate tablets. The recommended dose is one tablet per day of either Exforge/Ejocia 5/80mg, 5/160mg, 10/160mg, 5/320mg or 10/320mg.
ARTG number(s):	161825 and 161826

Product Background

Amlodipine is a calcium channel blocker and valsartan is an angiotensin II receptor blocker. Valsartan is registered in Australia as a monotherapy by Novartis Pharmaceuticals Australia Pty Ltd (Novartis) as the innovators, up to 320mg daily. However, amlodipine (approved up to 10mg daily) is not registered as a monotherapy from Novartis, but is sponsored by Pfizer as the innovator along with generic sponsors (there are no generic products containing valsartan). Monotherapy tablets containing amlodipine (as besylate) (5 mg and 10 mg) tablets were registered in Australia by Pfizer Australia Pty Ltd in June 1993 under the proprietary name Norvasc. These tablets are indicated for "*the first line treatment of hypertension. It 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 Norvasc, which has been used in combination with a thiazide diuretic, beta-adrenoreceptor blocking agent or an ACE inhibitor*" and "*the first line treatment of chronic stable angina. Norvasc may be used alone, as monotherapy or in combination with other antianginal drugs*".

The combination of amlodipine and valsartan is currently registered as Exforge or its additional name Ejocia in strengths of 5/80mg, 5/160mg and 10/160mg once daily for the treatment of hypertension as a second line indication. The current Australian submission is to register two higher strength combinations but using a different indication of replacement

therapy (also known as substitution therapy) for patients whose blood pressure is adequately controlled on amlodipine and valsartan used as individual tablets. As for the registered strengths, the proposed strengths will be indicated as a substitution therapy in patients (that is, patients are not to be started on this combination therapy).

There is a European Pharmacopoeia (EP)/British Pharmacopoeia BP 2009 monograph for amlodipine besilate[1] and a US Pharmacopoeia (USP) 32 monograph for amlodipine besylate, but no monographs for finished products containing this drug substance.

There are no BP monographs for valsartan or any dosage forms containing this drug substance, but there are USP 32 monographs for Valsartan drug substance and Valsartan and Hydrochlorothiazide Tablets. There are two specific TGA adopted European guideline relevant to this submission[2], besides the general guidelines. There is also a guideline[3] adopted by the European Medicines Agency (EMA) on substitution indications in cardiovascular treatments using products from different therapeutic classes which has not been adopted by the TGA.

Regulatory Status

Exforge (Ejocia) combination tablets are currently approved in Australia for the treatment of hypertension at strengths of 5/80 mg, 5/160 mg, and 10/160 mg, with the condition that treatment should not be initiated with the fixed dose combination. In addition, both amlodipine and valsartan are also registered in Australia for the treatment of hypertension at a maximum daily dose of 10 mg and 320 mg, respectively.

***Currently approved indication for 5/80, 5/160 and 10/160mg amlodipine: valsartan combinations In Australia**:*

> Exforge/Ejocia is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed dose combination.

The sponsor indicates that the amlodipine/valsartan 5/320 mg and 10/320 mg fixed combinations have been approved in the USA (20 June 2007) and Switzerland (22 December 2008) for the indication: *Treatment of essential hypertension. Exforge is indicated in patients whose blood pressure is not adequately controlled by monotherapy*). Applications to register the amlodipine/valsartan combination products have not been rejected in the USA or Canada. The USA approved indication is as follows:
Exforge (amlodipine and valsartan) is indicated for the treatment of hypertension. Exforge may be used in patients whose blood pressure is not adequately controlled on either monotherapy.

Exforge may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. The choice of Exforge as initial therapy for hypertension should be based on an assessment of potential benefits and risks including whether the patient is likely to tolerate the lowest dose of Exforge. Patients with stage 2 hypertension (moderate or severe) are at a relatively higher risk for cardiovascular events

[1] Note the Australian Approved Name (AAN) at the time of writing is Amlodipine Besylate and not Amlodipine Besilate.

[2] CPMP/EWP/240/95 Rev. 1: Fixed-Combination Medicinal Products. Effective: 12 February 2002.

And CPMP/EWP/238/95 Rev 2: Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension. Effective: 15 June 2006.

[3] CPMP/EWP/191583/2005. Guideline on the evaluation of medicinal products for cardiovascular disease prevention (see http://www.tga.gov.au/docs/pdf/euguide/ewp/31189007en.pdf).

(such as strokes, heart attacks, and heart failure), kidney failure and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and should be shaped by considerations such as baseline blood pressure, the target goal and the incremental likelihood of achieving goal with a combination compared to monotherapy. Individual blood pressure goals may vary based upon the patient's risk. Data from the high-dose multi-factorial study [see Clinical Studies (14)] provide estimates of the probability of reaching a blood pressure goal with Exforge compared to amlodipine or valsartan monotherapy. The figures below provide estimates of the likelihood of achieving systolic or diastolic blood pressure control with Exforge 10/320 mg, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modelling. The estimated likelihood at the right tail of each curve is less reliable due to small numbers of subjects with high baseline blood pressures.

Figure 1.

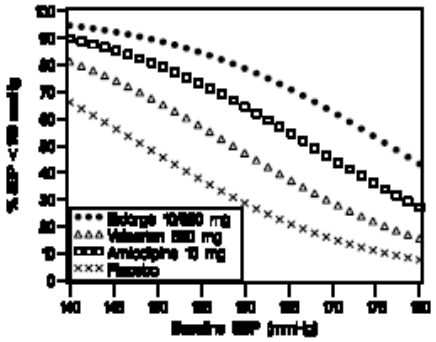


Figure 1: Probability of Achieving Systolic Blood Pressure <140 mmHg at Week 8

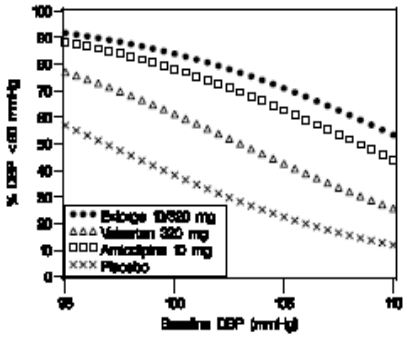


Figure 2: Probability of Achieving Diastolic Blood Pressure <90 mmHg at Week 8

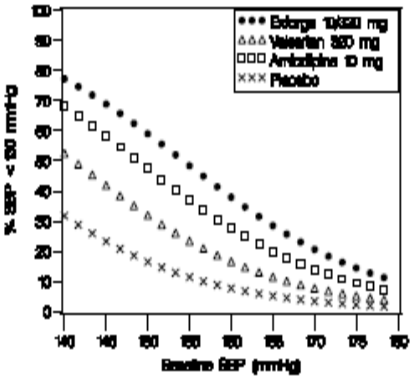


Figure 3: Probability of Achieving Systolic Blood Pressure <130 mmHg at Week 8

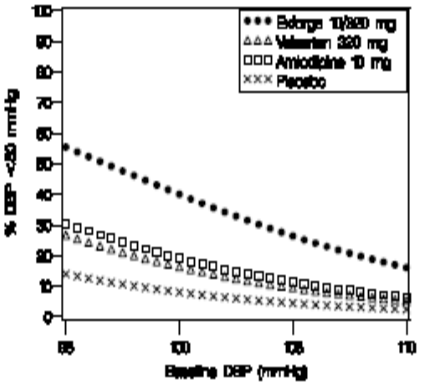


Figure 4: Probability of Achieving Diastolic Blood Pressure <80 mmHg at Week 8

For example, a patient with a baseline blood pressure of 160/100 mmHg has about a 67% likelihood of achieving a goal of <140 mmHg (systolic) and 80% likelihood of achieving <90 mmHg (diastolic) on amlodipine alone, and the likelihood of achieving these goals on valsartan alone is about 47% (systolic) or 62% (diastolic). The likelihood of achieving these goals on Exforge rises to about 80% (systolic) or 85% (diastolic). The likelihood of achieving these goals on placebo is about 28% (systolic) or 37% (diastolic).

Product Information

The approved Product Information (PI) document current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substances (active ingredients)

Compared to the registered strengths, an additional manufacturer of amlodipine is proposed. A European Directorate for the Quality of Medicines & HealthCare protects (EDQM) Certificate of Suitability (CEP) was provided for this drug substance from this site. Otherwise the details relating to the drug substances are identical to those already approved in Australia.

Drug Product

Formulation and manufacture

A dry granulation of valsartan and a dry granulation of amlodipine are compressed (using a double compression process). The tablets produced are film-coated and packed. This has resulted in a significant change in formulation (including the addition of sodium starch glycollate as a new excipient) compared to the registered strengths.

Specifications

Assay limits at expiry comply with TGO 56/78. There is no increase in the maximum daily dose with the increase in strength of valsartan and the limits for related substances relating to the registered strengths are still applicable. In fact the data indicates the limits can be lowered. The dissolution test differs from that used with the registered strengths, but has been justified.

Stability

The stability data provided will probably support a shelf life of 3/2.5 years (depending on strength) when stored below 25°C. It is being clarified how long bulk tablets may be stored at up to 40°C during transportation.

Bioavailability

The pivotal Phase III efficacy studies (A2307, A2307E1 and A2201) were performed with co-administration of single entity valsartan 160 mg capsules and amlodipine 5 and 10 mg capsules. Valsartan was dosed at both 160 and 320 mg (1 x and 2 x 160 mg).

- The 5 mg and 10 mg amlodipine capsules used in these studies were over-capsulated Norvasc tablets purchased in the US.
- The contents of the 160 mg valsartan capsules used in these studies were identical to the contents of the "Diovan" capsules registered in Australia.

Studies submitted

Two new bioavailability studies were provided. Each study used an appropriate study design and appropriately validated test methods for the determination of amlodipine and valsartan.

Study 2311 was an open-label, randomized, single dose, three-period, crossover pilot study to determine the relative bioavailability of 5/320 mg Prototype I and II formulations to a free combination of 5 mg amlodipine over-encapsulated tablets (Norvasc) and 320 mg valsartan capsules (2 x 160 mg Diovan). As mentioned above, the results from this study indicate that the valsartan response is lower in the tested fixed-dose combination tablets compared to the monotherapies.

Study 2310 was an open-label, randomised, single-dose, crossover, replicate study to demonstrate the bioequivalence between the **proposed** fixed-dose combination of 5/320 mg tablet and the free combination of clinical service formulations of 2 x 160 mg valsartan capsules (Diovan)[4] and 5 mg amlodipine over-encapsulated tablets (Norvasc). Note that the monotherapies were used in the Phase III clinical studies. Results from the study indicated that:

- For valsartan the rate and extent of absorption from the fixed combination tablet are equivalent to those of the free combination treatment.
- For amlodipine the rate and extent of absorption from the fixed combination tablet are equivalent to those of the free combination treatment[5,6].

Note the sponsor also referred to three other bioavailability studies and a pharmacokinetics (PK) interaction study which were evaluated in relation to the submission to register the lower strength products. These are summarised below.

Study 2302 was a pilot bioavailability study utilised to help develop the final market image (FMI) tablets. The study was an open-label, single-dose, three-period, randomised crossover study investigating the relative bioavailability of 10/160 mg and 2.5/80 mg prototype fixed combination tablet formulations, compared to the free combination of 10 mg amlodipine (Norvasc) and 160 mg valsartan (Diovan) tablets. On the basis of the results, the prototype tablets were manufactured and used in the pivotal bioequivalence (BE) studies (#2303 and #2309).

Study 2303 was an open-label, single-dose, two-treatment, four-period, randomised crossover, replicate study investigating the bioequivalence between the fixed combination of 2.5/80 mg tablet and the free combination of 2.5 mg over-encapsulated amlodipine tablets (Norvasc) and 80 mg valsartan capsules (Diovan). The results indicate that the rate and extent of absorption of the fixed and free combinations are sufficiently similar, except that the maximum plasma concentration (C_{max}) of valsartan was 17 % higher with the fixed combination treatment compared to that of the free combination treatment. The 2.5/80 tablet is not registered in Australia.

Study 2309 was an open-label, single-dose, two-treatment, four-period, randomised crossover, replicate study investigating the bioequivalence between the fixed combination of FMI 10/160 mg tablets and the free combination of the 160 mg valsartan capsule (Diovan) and the 10 mg amlodipine over-encapsulated tablets (Norvasc). The results indicate that the rate and extent of absorption of the fixed and free combinations are equivalent, allowing extrapolation of the safety and efficacy data from the Phase III trials to the FMI tablet.

Protocol 37 was a PK drug-drug interaction study investigating the pharmacokinetic parameters of single dose of 5 mg amlodipine over-encapsulated tablets (Norvasc) and the 160 mg valsartan capsule (Diovan) and the combination of amlodipine 5 mg and valsartan 160 mg. This was a randomised, open label, three-way, crossover trial. Results indicate that there is no interaction between amlodipine and valsartan, except a slight drop (15%) in C_{max} of valsartan from a possible effect of amlodipine.

[4] It has previously been demonstrated that 2 x 160 mg tablets are bioequivalent to 1 x 320 mg tablet.

[5] Note the batch assay of the amlodipine monotherapy product was unknown, but calculations indicate that using worst case results did not alter the conclusions of the study.

[6] Note (also) that there was an unusual result in that one subject had a very high plasma result at 49 hours for amlodipine. Recalculating the 90% confidence intervals after removal of this subject did not alter the conclusions of the study.

These studies are discussed further under the heading *IV Clinical Findings, Pharmacokinetics* below.

Justifications submitted for non-supply of bioavailability/bioequivalence data

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

The company referred to previously provided justifications for using the overseas amlodipine products in the bioavailability and clinical studies rather than products available in Australia. Those justifications are relevant to this submission and acceptable. In particular, it should be noted that the dissolution profiles of amlodipine at pH 1.2, 4.5 and 6.8 from the proposed fixed-dose combination tablets are very similar to the dissolution profiles from Norvasc tablets purchased in Australia, and that amlodipine can be considered Biopharmaceutical Classification System Class 1 (high solubility /high permeability)[7].

Previous Consideration by the Pharmaceutical Subcommittee of ADEC

Details of this submission were presented at the 131st meeting of the Pharmaceutical Subcommittee (PSC) of ADEC (Australian Drug Evaluation Committee now called Advisory Committee for Prescription Medicines (ACPM)) in March 2010. The PSC had reservations regarding:

- The confidence in the conclusions in relation to amlodipine from study 2310 due to the unusual result for one subject at 49 hours.
- Justification for using the overseas amlodipine product in the Phase III efficacy and bioavailability studies.

The PSC did not require review of this submission again. These issues were resolved to the satisfaction of the TGA.

Recommendation and Comments

Approval of the company's application is recommended with respect to chemistry and quality control. With respect to bioavailability, data were provided that demonstrated bioequivalence of amlodipine and valsartan when administered as the fixed-dose combination amlodipine and valsartan tablets to amlodipine and valsartan when administered as a co-administration of monotherapy products.

III. Nonclinical Findings

There were no nonclinical data submitted with the current Australian submission.

IV. Clinical Findings

Introduction

The sponsor states that the data package provided to the TGA to support the registration of amlodipine/valsartan 5/320 mg and 10/320 mg combinations is identical to that submitted in Switzerland and "essentially similar" to that submitted to the US. The clinical data relating specifically to the current submission to register amlodipine/valsartan 5/320 mg and 10/320

[7] 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.

mg combination tablets included two bioequivalence studies [2311; 2310] and three clinical efficacy and safety studies [2201; 2307; 2307E1]. These five studies have been previously submitted to the TGA to support the sponsor's original application to register Exforge 5/80 mg, 5/160 mg, and 10/160 mg combination tablets, and have been previously evaluated by the TGA and the ADEC [255th Meeting].

In addition to the five studies specifically relating to registration of the amlodipine/valsartan 5/320 mg and 10/320 mg combination tablets, the submission also included all previously submitted and evaluated studies relating to the 5/80 mg, 5/160 mg and 10/160 mg combination tablets. The five studies relating specifically to the current submission have been re-evaluated [2311; 2310; 2201; 2307; 2307 E1]. The two, randomized, placebo-controlled, 8-week, double-blind efficacy and safety studies included data on the amlodipine/valsartan 5/320 mg combination [2201] and the amlodipine/valsartan 10/320 mg combination [2301]. The open-label, 54-week, extension study [2307E1] included long-term efficacy and safety data on amlodipine/valsartan 5/320 mg. The bioequivalence study [2310] included comparative bioavailability data on the amlodipine/valsartan 5/320 mg fixed combination tablet proposed for registration and on amlodipine 5 mg (over-encapsulated tablet) and valsartan 320 mg (2 x 160 mg capsules) administered concomitantly. The bioequivalence study [2311] included bioavailability data on two prototype fixed combination amlodipine/valsartan 5/320 mg tablets and their components. The original submission also included one pharmacokinetic study [37] which investigated potential interactions between valsartan 160 mg and amlodipine 5 mg. Relevant results from this study have been referred to in the current clinical evaluation although it has not been fully re-evaluated. The sponsor also provided a justification for not submitting a bioequivalence study evaluating the proposed amlodipine/valsartan 10/320 mg fixed combination tablet and this justification has been reviewed. The original submission also included three active-controlled efficacy and safety studies [2305; 2306; 2308] and an open-label, long-term extension study [2201E]. None of these four studies included data on the proposed amlodipine/valsartan 5/320 mg and 10/320 mg combinations. Consequently, none of these four studies have been re-evaluated. The original submission also included three bioequivalence studies [2302; 2303; 2309], none of which have been re-evaluated as they included amlodipine/valsartan combinations other than 5/320 mg or 10/320 mg.

Pharmacokinetics

Overview

The submission included two bioequivalent studies investigating a single fixed dose combination of amlodipine/valsartan 5/320 mg and a single dose free combination of amlodipine 5 mg and valsartan 320 mg [studies 2310 and 2311]. *Study 2311* was a pilot bioavailability study in healthy adults comparing two mono-layer prototype amlodipine/valsartan 5/320 mg fixed dose tablets with free combination amlodipine 5 mg tablets (Norvasc, US sourced) and valsartan 320 mg tablets (Diovan, US sourced). The sponsor indicates that neither of the 5/320 mg fixed dose tablets used in the pilot study are identical to that proposed for Australian registration. The results showed that for both of the prototype 5/320 mg fixed dose tablets the 90% confidence intervals for the geometric mean ratios (fixed/free) for the maximum plasma concentration (C_{max}) and area under the plasma drug concentration versus time curve from zero to time t (AUC_{0-t}) for valsartan were outside the accepted bioequivalence interval of 0.80 to 1.25. The geometric mean valsartan C_{max} values were 21% and 12% lower with fixed prototypes 1 and 2, respectively, compared with the free combination. The geometric mean valsartan AUC_{0-t} values were 17% and 10% lower with fixed prototypes 1 and 2, respectively, compared with the free combination. The results for amlodipine showed that both fixed prototypes and the free combination were

bioequivalent with respect to both the C_{max} and AUC_{0-t}. In view of the *study 2311* results the formulations of the amlodipine/valsartan 5/320 mg and 10/320 mg fixed dose combination tablets were changed from mono-layer to bi-layer. The results from *study 2311* have been examined but the study has not been fully evaluated as the formulations of the fixed-dose amlodipine/valsartan 5/320 mg tablets used in this study differed from the formulation being proposed for registration. The results for *study 2311* are summarised in Table 1.

Table 1: Study 2311 – Pharmacokinetic parameters of valsartan and amlodipine following fixed 5/320 mg combination tablet prototypes (test) and free combination (reference) amlodipine 5 mg and valsartan 320 mg.

Valsartan/ Amlodipine	Analyte	Pharmacokinetic Parameter	Treatment	Geometric mean (N*)	Ratio of geometric means (test/reference)**	90% CI for ratio ***
320/5 mg Fixed Combination (Prototype I)	Valsartan	AUC_{0-t}	Test Reference	43.1 51.6	0.83	(0.71, 0.99)
		C_{max}	Test Reference	5.4 6.9	0.79	(0.63, 0.98)
	Amlodipine	AUC_{0-t}	Test Reference	109.3 109.9	0.99	(0.93, 1.06)
		C_{max}	Test Reference	2.4 2.4	1.01	(0.94, 1.09)
320/5 mg Fixed Combination (Prototype II)	Valsartan	AUC_{0-t}	Test Reference	46.3 51.6	0.90	(0.76, 1.06)
		C_{max}	Test Reference	6.1 6.9	0.88	(0.71, 1.10)
	Amlodipine	AUC_{0-t}	Test Reference	109.2 109.9	0.99	(0.93, 1.06)
		C_{max}	Test Reference	2.4 2.4	0.99	(0.92, 1.07)

In *study 2310*, the bioequivalence of the final market image (FMI) of the amlodipine/valsartan 5/320 mg fixed dose tablet and the free combination of amlodipine 5 mg (over-encapsulated 5 mg tablet) and valsartan 320 mg (2 x 160 mg capsules) was investigated in healthy adults. The 5/320 mg fixed dose combination tablet used in this study is stated by the sponsor to be that proposed for Australian registration, while the amlodipine 5 mg over-encapsulated tablet was sourced from the US (Norvasc) and the valsartan 160 mg capsule was sourced from Switzerland. The sponsor states that it has submitted data in previous applications demonstrating bioequivalence of the valsartan capsules used in the clinical program for the fixed-dose combination tablets and valsartan (Diovan) formulations registered in Australia. The sponsor also states that it has not undertaken a bioequivalence study comparing the amlodipine 5 mg tablet (Norvasc) used in this study with the Australian registered amlodipine 5 mg tablet (Norvasc). However, the potential bioavailability difference between US sourced and Australian registered amlodipine 5 mg (Norvasc) tablets was considered by the ADEC and satisfactorily resolved (ADEC minutes, 255th meeting). The ADEC minutes indicate that amlodipine is considered to be a BCS Class 1 drug with high solubility and permeability. Consequently, there are unlikely to be significant differences between the bioavailability of the amlodipine 5 mg tablet used in *study 2310* and the Australian registered amlodipine 5 mg tablet. *Study 2310* has been fully re-evaluated (see below).

The submission did not include a bioequivalence study investigating amlodipine/valsartan 10/320 mg fixed dose combination tablets and free combination amlodipine 10 mg and

valsartan 320 mg. However, the sponsor submitted a justification seeking a "biowaiver" and this is considered below. The submission did not include bioequivalence studies investigating the proposed amlodipine/valsartan 5/320 mg and 10/320 mg fixed dose combinations in patients with hypertension.

Study 2310 – Bioequivalence Study

Objectives

The primary objective of *study 2310* was to demonstrate the bioequivalence of a fixed combination amlodipine/valsartan 5/320 mg final market image (FMI) tablet and a free combination of amlodipine 5 mg tablets (over-encapsulated) and valsartan 320 mg (2 x 160 mg capsules). The secondary objectives of the study were to demonstrate the safety and tolerability of the 5/320 mg fixed combination.

The study was conducted in a single centre (in Texas, USA) from April to June 2005. The study protocol was reviewed by an Independent Investigational Review Board (IRB). The study was conducted in compliance with Good Clinical Practices (GCP) and according to the ethical principles of the Declaration of Helsinki. All subjects gave written informed consent.

Methodology

The study was open-label, randomized, single-dose, four-period, cross-over and replicate in design. It was undertaken in healthy subjects of both sexes aged from 18 to 45 years. The inclusion and exclusion criteria were typical of PK studies in healthy volunteers. Each subject participated in a 21-day screening period, four treatment periods, and an end-of-study evaluation. The four treatment periods consisted of two fasted treatments (A and B) given twice: treatment A (test) consisted of a single dose of the 5/320 mg fixed combination tablet stated by the sponsor to be identical to the formulation proposed for registration; and treatment B (reference) consisted of free combination amlodipine 5 mg (tablet [over-encapsulated capsule]) and valsartan 320 mg (2 x 160 mg capsules). There was at least a 14 day wash-out period between treatments and subjects were randomized equally to sequence ABAB or BABA. In each treatment period, subjects were admitted to the study site at least 12 hours prior to dosing and remained in the site for at least 48 hours after dosing, and returned to the site at 72, 96, 144 and 168 hours after dosing.

Blood was collected to measure plasma valsartan concentration pre-dose and then post-dose at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours. The half-life of valsartan is 9.5 hours (Diovan PI) and, consequently, blood sampling to 48 hours (> than 3 half-lives) is sufficient to adequately characterize the valsartan plasma concentration versus time-profile. In addition, the valsartan half-life supports the 14 day (> 3 half-lives) washout between treatments. Blood was collected to measure plasma amlodipine concentration pre-dose and the post-dose at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 144 and 168 hours. The half-life of amlodipine is 30 to 50 hours (Norvasc PI) and, consequently, blood sampling to 168 hours (> 3 half-lives) is sufficient to adequately characterize the amlodipine plasma concentration versus time-profile. In addition, the amlodipine half-life supports the 14 day (> 3 half-lives) washout between treatments. Plasma valsartan and amlodipine concentrations were determined by two different liquid chromatography-mass spectrometry mass (LC-MS-MS) methods. The lower limit of quantitation (LLOQ) of valsartan was 20 ng/mL using 100 µL plasma, and the LLOQ of amlodipine was 0.075 ng/mL using 0.5 mL plasma.

Plasma concentration versus time-profiles were used to determine $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ (area under the plasma drug concentration versus time curve from time 0 to infinity), C_{max}, time to maximum concentration of drug in plasma/serum (t_{max}), and half-life ($t_{½}$), in all subjects for both valsartan and amlodipine, using non-compartmental methods. The PK parameters of

valsartan and amlodipine were compared between the free combination (reference) and the fixed combination (test). Log-transformed AUC and C_{max} were analyzed by a linear mixed effects model, with fixed effects for sequence, treatment, and period, and random effect for subject by treatment interaction. The 90% confidence intervals (CIs) of the treatment mean ratios were used to evaluate the bioequivalence of the fixed combination (test) and the free (reference) formulations. All subjects who completed at least two periods of the study and had data for both treatments were included in the PK analysis. A total of 54 subjects completed all four periods and 61 subjects had PK data from at least 2 periods (AB or BA). A sample size of 56 subjects was sufficient to provide an 80% power to demonstrate bioequivalence if the true difference was approximately 10% based on a co-efficient of variation of approximately 40% (an estimate based on the results from *study 2309*).

Subjects

The study enrolled 64 healthy subjects of whom 53 completed the study in compliance with the protocol and 11 discontinued. The reasons for discontinuation were: adverse events (2 subjects); protocol violation (3 subjects); withdrawn consent (5 subjects); and "administrative issues" (1 subject). Of the 64 enrolled subjects, 44 (68.8%) were male, 20 were female (31.3%), mean±standard deviation (SD) age was 32.5±7.61 years, mean±SD weight was 79.95±14.66 kg, and mean±SD height was 173.7±9.1 cm. The racial background of the 64 enrolled subjects was Caucasian (n=27, 44.2%), black (n=25, 39.1%), and other (n=12, 18.7%).

Pharmacokinetic Results

Valsartan - The key PK results for valsartan are summarised below in Table 2. The 90% confidence intervals for the ratio of geometric means (fixed/free) for valsartan C_{max} and AUC were completely within the accepted bioequivalence range of 0.80 to 1.25. The results for the arithmetic mean and median valsartan PK showed that valsartan t_{max} and $t_{1/2}$ values were similar for both the fixed and free combination treatments. The mean AUC_{0-t} was greater than 80% of the mean AUC_{0-inf} for both treatments indicating that sampling time was sufficient to adequately characterize the valsartan plasma concentration versus time-profile. The valsartan plasma concentration time profile is provided in Figure 2. It shows that the profiles for valsartan are virtually identical following the fixed and free combination treatments.

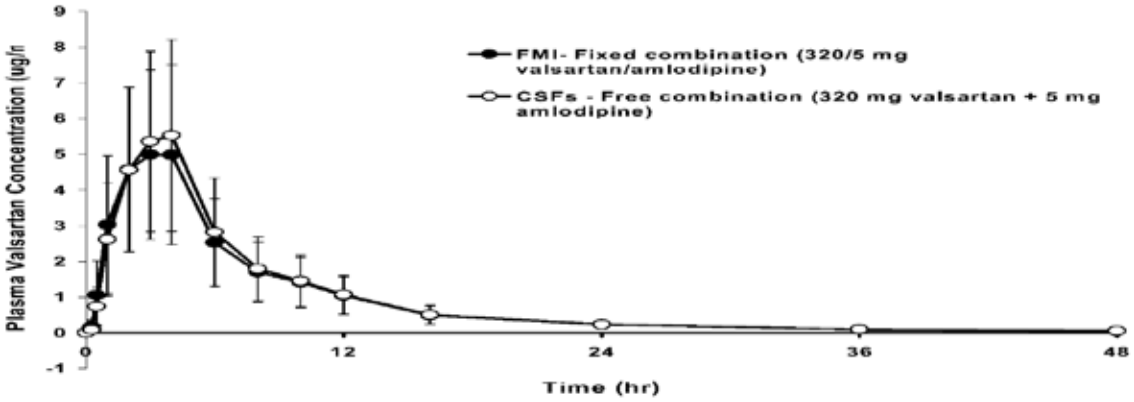
Table 2: Valsartan – key pharmacokinetic results.

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (µg/mL)	Fixed (fixed)*	5.2	0.91	0.85 – 0.98
	Free (reference)**	5.7		
AUC_{0-t} (h*µg/mL)	Fixed (test)*	37.9	0.95	0.90 – 1.00
	Free (reference)**	39.8		
$AUC_{0-\infty}$ (h*ng/mL)	Fixed (test)*	38.9	0.95	0.91 – 1.00
	Free (reference)**	40.8		

*Fixed is the test treatment: 320/5 valsartan/amlodipine final market image (FMI) combination tablet.

**Free is the reference treatment: 320/5 free combination of 160 mg valsartan CSF capsules and 5 mg amlodipine CSF capsule.

Figure 2: Study 2310 – Mean±SD plasma concentration-time profiles for valsartan.



Amlodipine - The key PK results for amlodipine are summarised below in Table 3. The 90% confidence intervals for the ratio of geometric means (fixed/free) for amlodipine C_{max} and AUC were completely within the accepted bioequivalence range of 0.80 to 1.25. The results for arithmetic mean and median amlodipine PK parameters showed that amlodipine t_{max} and $t_{1/2}$ values were similar for both the fixed and free combination treatments. The mean AUC_{0-t} was greater than 80% of the mean AUC_{0-inf} for both treatments indicating that sampling time was sufficient to adequately characterize the amlodipine plasma concentration versus time-profile. The amlodipine plasma concentration time profile is provided in Figure 3. It shows that the profiles for amlodipine are virtually identical following the fixed and free combination treatments.

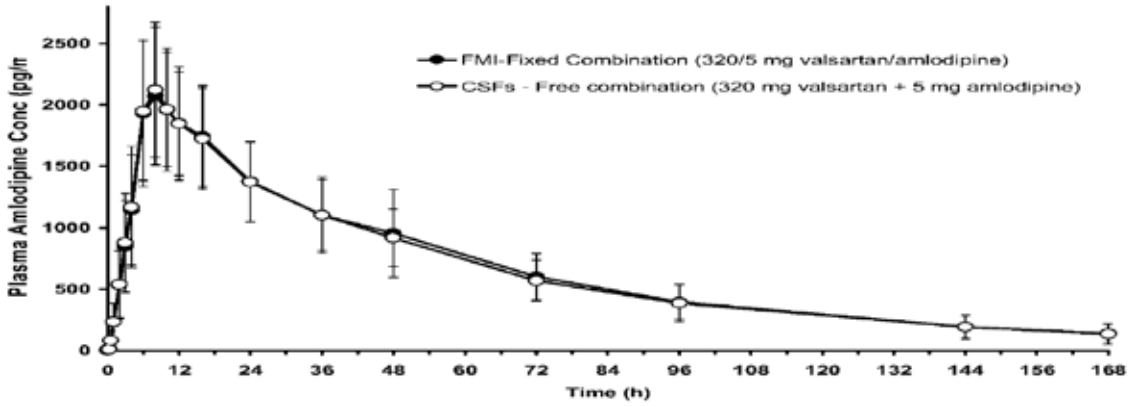
Table 3: Amlodipine – key pharmacokinetic parameters.

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (pg/mL)	Fixed (fixed)*	2111.7	0.99	0.97 – 1.02
	Free (reference)**	2122.7		
AUC_{0-t} (h*pg/mL)	Fixed (test)*	107274.0	0.99	0.96 – 1.02
	Free (reference)**	107966.0		
$AUC_{0-\infty}$ (h*pg/mL)	Fixed (test)*	117567.4	1.01	0.99 – 1.03
	Free (reference)**	116640.4		

*Fixed is the test treatment: 320/5 valsartan/amlodipine final market image (FMI) combination tablet.

**Free is the reference treatment: 320/5 free combination of 160 mg valsartan CSF capsules and 5 mg amlodipine CSF capsule.

Figure 3: Study 2310 – Mean±SD plasma concentration-time profiles for amlodipine.



Safety Results

The 53 subjects who completed the study in compliance with the protocol received two single doses of the 5/320 mg fixed combination and two single doses of the free combination of 5 mg amlodipine and 320 mg (2 x 160 mg) valsartan. Of the 64 enrolled subjects, 21 (32.8%) treated with the fixed combination experienced at least one adverse event compared with 17 (26.6%) treated with the free combination. The most frequent adverse event (AE) in both treatment groups was headache which occurred in 5 subjects (7.8%) following both the fixed and free combinations. The other AEs occurring in more than 3% of subjects in either treatment groups were (fixed versus free): dizziness (4.7% versus 0%); hot flush (4.7% versus 0%); diarrhoea (1.6% versus 3.1%); dysgeusia (1.6% versus 3.1%); pollakiuria (3.1% versus 1.6%); and upper abdominal pain (3.1% versus 0%). No serious adverse events or deaths were reported during the study. There were two discontinuations due to AEs (1 x pregnancy, 1 x moderate headache). There were no significant changes in laboratory parameters, vital signs, or electrocardiographs (ECGs).

Comment

This was a good quality PK study. It showed that a single dose fixed combination of an amlodipine/valsartan 5/320 mg tablet (FMI) and a single dose free combination of amlodipine 5 mg (tablet over-encapsulated) and valsartan 320 mg (2 x 160 mg capsule) were bioequivalent as regards both amlodipine and valsartan. The fixed-dose combination amlodipine/valsartan 5/320 mg tablet used in the study is stated by the sponsor to be identical to that proposed for Australian registration. The amlodipine 5 mg tablet (Norvasc, US) used in the study was not the Australian registered product, but it is reasonable to conclude that there are unlikely to be clinically significant bioavailability differences between the two products (see above). Based on information provided by the sponsor, the valsartan 160 mg capsules used to administer the 320 mg dose in the study are bioequivalent to Australian registered valsartan (Diovan) products. Consequently, it is reasonable to assume that the 2 x 160 mg valsartan capsules used in the study are bioequivalent to Australian registered 320 mg valsartan (Diovan) tablets. Overall, the study is considered to satisfactorily demonstrate that patients being treated with Australian registered amlodipine 5 mg and valsartan 320 mg tablets can safely switch to the proposed amlodipine/valsartan 5/320 mg combination tablet without adverse pharmacokinetic consequences.

No Bioequivalence Study (10/320 mg) – Comments on Justification

Overview

The submission did not include a bioequivalence study comparing the fixed combination of amlodipine/valsartan 10/320 mg and the free combination of amlodipine 10 mg and valsartan 320 mg. However, the sponsor provided a justification for not providing such a study, and this justification is considered below.

· Nature of the dosage form: The sponsor states that "the Exforge/Ejocia film-coated tablets are orally available, immediate release tablets containing two ingredients, forms of which are registered in Australia". *Comment: This is acceptable as there are immediate release oral forms of valsartan 320 mg, amlodipine 5 mg and amlodipine 10 mg registered in Australia, and the proposed combination tablets are immediate release.*

· Solubility of the active ingredients: The sponsor states that ".. Valsartan is very slightly soluble in water (0.18 g/L) and in acidic media (0.1 g/L, 0.1M hydrochloric acid (HCl)). The solubility of valsartan in 0.0067 in phosphate buffer, pH 8.0 is 16.8 g/L .... [and] .... Amlodipine besylate is slightly soluble in water and its solubility in the pH conditions

relevant to gastrointestinal (GI) fluids is approximately 1 mg/mL". *Comment: These statements should be confirmed by the quality evaluator.*

· Comparative dissolution profiles across the physiological pH range (1-7.5): The sponsor states that the "dissolution profiles of valsartan and amlodipine in Exforge/Ejocia 5/320 mg and 10/320 mg are comparable in pH 1.0, pH 4.5 and pH 6.8 media". *Comment: The dissolution profiles have been examined and are considered to be comparable. However, this is primarily a matter for the quality evaluator.*

· Pharmacokinetic Characteristics of the Active Ingredients: The sponsor states that "valsartan and amlodipine exhibit linear pharmacokinetics in the approved dose range. There is no pharmacokinetic interaction between valsartan and amlodipine (Protocol 37)." *Comment: The valsartan (Diovan) PI states that the pharmacokinetics of the drug are linear over the dose range 80 to 320 mg. However, the amlodipine (Norvasc) PI is silent on the linearity of the pharmacokinetics of the drug. The European Medicines Agency (EMA)* European Public Assessment Report (EPAR) document for Exforge states that both va*lsartan and amlodipine "exhibit linear and dose proportional pharmacokinetics". Review of the results for Protocol 37 showed that the 90% confidence intervals for the log-transformed values for the ratios ([amlodipine 5 mg + valsartan 160 mg]/[amlodipine 5 mg alone]) for amlodipine AUC_{0-t}, AUC_{0-inf}, and C_{max} were completely within the accepted bioequivalence range of 0.80 to 1.25. These results confirm that valsartan 160 mg has no significant effects on the pharmacokinetics of amlodipine 5 mg. The 90% confidence intervals for the log-transformed values for the ratios ([amlodipine 5 mg + valsartan 160 mg]/ [valsartan 160 mg alone]) for valsartan AUC_{0-t} and AUC_{0-inf} were completely within the accepted bioequivalence range of 0.80 to 1.25, while the 90% CI [0.69, 1.04] for the corresponding C_{max} ratio was outside the accepted bioequivalence range of 0.80 to 1.25. However, this observed difference in the valsartan C_{max} between valsartan alone and valsartan in combination with amlodipine is unlikely to be clinically significant. Overall, the sponsor's statement is considered to be acceptable.*

· Clinical Consequences of Any Potential Differences in Bioavailabilities of the Products under Consideration. The sponsor states that "[B]oth ingredients have wide therapeutic indices. There is little risk of any significant clinical consequence in the case of variable bioavailability. Furthermore, the enclosed dossier includes extensive Phase III safety and efficacy data on the combinations sought. Finally, Exforge/Ejocia is intended to be available in three dosage strengths, allowing for dose adjustment where required". *Comment: The sponsor's statements are considered acceptable. However, with the addition of the combinations 320/5 mg and 320/10 mg there will now be five combination tablets available rather than three.*

· Width of the margin between the minimum effective and minimum toxic plasma concentrations. The sponsor states that "[T]here is a wide margin of safety between efficacy and toxicity for both ingredients. Valsartan is registered up to 320 mg for the treatment of hypertension. Amlodipine is registered up to 10 mg. Furthermore, the present dossier includes extensive safety and efficacy data on the combinations sought". *Comment: The sponsor's statements are considered acceptable.*

· The similarities of, or differences between, the formulations being considered: The sponsor states that "[T]he compositions of the 5/320 mg and 10/320 mg FMI tablets are identical apart from the dose adjustment of amlodipine ..... bioequivalence with the 5/320 mg FMI tablets has been established. Furthermore, the manufacturing processes are identical". *Comment: The tablet core layers are identical apart from the dose of amlodipine, but the compositions of the coatings differ as regards colouring. The sponsor's statements on*

composition and manufacturing are primarily matters for the quality evaluator, but appear to be acceptable.

Overall Comment

The issue is whether patients stabilized on amlodipine 10 mg and valsartan 320 mg will experience a pharmacokinetic interaction when switched to the amlodipine/valsartan 10/320 mg fixed combination tablet. *Study 2310* demonstrated that the amlodipine/valsartan 5/320 mg fixed combination tablet and the free combination of amlodipine 5 mg (tablet over-encapsulated) and valsartan 320 mg (2 x 160 mg capsules) were bioequivalent. The clinical aspects of the justification for not submitting a bioequivalence study for the amlodipine/valsartan 10/320 mg combination tablet are considered acceptable.

Drug Interactions

No new data.

Pharmacodynamics

No new data.

Efficacy

Overview

There were two, placebo-controlled studies consisting of 8-weeks of double-blind treatment in patients with mild to moderate hypertension considered to be central to the current submission [2201; 2307]. Study 2201 included efficacy and safety data on the combination valsartan/amlodipine (val/aml) 320/5 mg administered as 2 x 160 mg valsartan capsules plus 1 x 5 mg amlodipine capsule (over-encapsulated 5 mg tablet) in 127 randomized patients. Study 2307 included efficacy and safety data on the combination valsartan/amlodipine 320/10 mg administered as 2 x 160 mg valsartan capsules plus 2 x amlodipine 5 mg capsules (over-encapsulated 5 mg tablets) in 210 randomized patients. In neither of the two placebo-controlled studies were patients stabilized on valsartan 320 mg and amlodipine 5 mg or 10 mg before being switched to the corresponding fixed combination. However, the design of both placebo-controlled studies was in accordance with the TGA adopted EMA Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension (CPMP/EWP/238/95 Rev 2). There was one long-term, open-label, 54 week-extension efficacy and safety study directly relevant to the submission [2307E1]. This study provided data on combined valsartan/amlodipine 320/5 mg administered as 2 x 160 mg valsartan capsules and 1 x 5 mg amlodipine capsule (over-encapsulated 5 mg tablet) in 403 patients with mild to moderate hypertension recruited from study 2307. None of the three efficacy and safety studies utilized the valsartan/amlodipine 320/5 mg or 320/10 mg combination tablets proposed for registration. Instead, valsartan and amlodipine capsules of identical appearance were administered concomitantly. The amlodipine capsules were over-encapsulated amlodipine tablets (Norvasc, US).

The results of study 2201 and study 2307 have been published[8]. This publication was not provided in the submitted references, presumably because it was published after compilation of the submitted clinical reference list.

[8] Philipp T, Smith TR, Glazer R et al. 2007. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. *Clinical Therapeutics* 29(4):563-580.

Study 2201 and Study 2307

Objectives

The primary objective of both study 2201 and study 2307 was to assess the blood pressure lowering effects of a once daily (OD) regimen of various combinations of valsartan and amlodipine, compared with their monotherapy components and placebo, in patients with uncomplicated, essential, mild to moderate diastolic hypertension (mean sitting diastolic blood pressure [MSDBP] $\geq$ 95 mmHg and <110 mmHg). The treatments of particular interest for the current submission were valsartan/amlodipine 320/5 mg, valsartan 320 mg, amlodipine 5 mg, and placebo in study 2201, and valsartan/amlodipine 320/10 mg, valsartan 320 mg, amlodipine 10 mg, and placebo in study 2307. Evaluation of the studies has centred on these treatments of interest.

The secondary objectives of study 2201 were to determine the best dose combination of valsartan and amlodipine compared with monotherapy, and to assess the safety and tolerability of the combination of valsartan and amlodipine in patients with essential diastolic hypertension. The secondary objectives of study 2307 were to determine the blood pressure lowering effects of once daily various combinations of valsartan and amlodipine, compared with their monotherapy components and placebo on systolic blood pressure, and to assess the safety and tolerability of the combination of valsartan and amlodipine in patients with essential diastolic hypertension.

Conduct of the Studies

Both studies were performed in accordance with standard operating procedures of Novartis (the sponsor). The studies were designed to ensure adherence to GCP and in compliance with the Declaration of Helsinki and relevant European Community and US legislation and directives relating to the conduct of clinical trials. In each study all patients gave written informed consent.

Study 2201 was conducted in 169 centers in 6 countries (7 in Belgium, 10 in Canada, 7 in France, 32 in Germany, 5 in Mexico and 108 in the US). The first patient was enrolled in January 2003 and the last patient completed in February 2004. Study 2307 was conducted in 133 centers in 10 countries (2 Egypt, 9 France, 84 Germany, 10 Korea, 2 Malaysia, 4 Norway, 6 Peru, 1 Portugal, 10 Spain and 5 in Taiwan). The first patient was enrolled in January 2004 and the last patient completed in July 2004. None of the study centres in either study were located in Australia.

Methodology

Both studies were multinational, multicenter, double-blind, randomized, multi-factorial, placebo-controlled and parallel group in design. In both studies there was a 2-week washout period to allow patients to discontinue previous anti-hypertensive medication, followed by a 2 to 4 week single-blind placebo run-in period immediately preceding randomization, and an 8-week double-blind treatment period. The visit schedule for study 2201 was similar to that for study 2307.

In study 2201, there were 15 treatment groups and patients randomized to the valsartan/amlodipine 320/5 mg OD treatment group were force-titrated to this combination after one week of double-blind treatment with valsartan/amlodipine 160/2.5 mg OD. In study 2307, there were 6 treatment groups and patients randomized to the valsartan/amlodipine 320/10 mg OD treatment group were force-titrated to this combination after one week of double-blind treatment with valsartan/amlodipine 160/5 mg OD. In neither study were patients stabilized on valsartan 320 mg and amlodipine 5 mg or valsartan 320 mg and amlodipine 10 mg switched to the corresponding fixed combination tablet. In both studies, combination valsartan/amlodipine treatments consisted of separate valsartan and amlodipine capsules administered concomitantly, and placebo treatment consisted of matching capsules.

The inclusion and exclusion criteria were similar for both studies. The inclusion criteria included male and female outpatients at least 18 years of age with uncomplicated essential diastolic hypertension (MSDBP≥ 95 mmHg and < 110 mmHg). Patients were required to have a MSDBP ≥ 90 mmHg and < 110 mmHg at Visit 1 (Week -4 to -2), and a MSDBP ≥ 95 mmHg and < 110 mmHg at Visit 2 (randomization, Week 0). In addition, patients were required to have an absolute difference of≤ 10 mmHg in average sitting diastolic blood pressure between Visit 1 and 2. The exclusion criteria included patients with severe hypertension (MSDBP ≥ 110 mmHg and/or MSSBP ≥ 180 mmHg), secondary hypertension, and various cardiovascular and cerebrovascular conditions. The exclusion criteria were comprehensive and typical for studies of this type.

In both studies, concomitant treatment with anti-hypertensive medications was excluded from the beginning of the wash-out period to the end of the double blind period. There were a number of medications which were excluded or, if ethically justified, were gradually withdrawn before randomization. The list of excluded medicines in study 2201 is similar to that in study 2307.

Efficacy Variables

The efficacy variables were the same for both studies. The primary efficacy variable was the change from baseline in the mean sitting diastolic blood pressure at study endpoint. The secondary efficacy variables were change from baseline in the mean sitting systolic blood pressure; response rates defined as the proportion of patients achieving a mean sitting diastolic blood pressure of < 90 mmHg or a≥ 10 mmHg decrease compared with baseline; and control rates defined as the proportion of patients achieving a mean sitting diastolic blood pressure of < 90 mmHg. Other efficacy variables included change from baseline in standing systolic and diastolic blood pressure, and change from baseline in sitting and standing pulse rate.

Blood pressure was measured at the beginning of the single-blind, placebo-run in period, at randomization, and after Weeks 2, 4, 6, and 8 of the double-blind treatment period. It was measured with a calibrated standard aneroid or mercury sphygmomanometer and appropriate cuff size. The arm in which the highest sitting diastolic blood pressures were found at Visit 1 (that is, the beginning of the single-blind, placebo run-in) was the arm used for all subsequent

readings. The blood pressure was measured three times at 1 to 2 minute interval after first sitting for 5 minutes. The mean of the three sitting blood pressure measurements was used as the measurement for that visit. Following assessment of the sitting blood pressure, one standing blood pressure measurement was taken after standing for 2 minutes. Ideally, at every visit the blood pressure was measured by the same staff member at the same time of day, using the same equipment

Statistical Methods and Sample Size

The statistical methods were the same for both studies. The intention-to-treat (ITT) population was the primary population for analysis of efficacy, with analysis also being undertaken in the per-protocol (PP) population. The ITT population included all randomized patients with at least one post-baseline blood pressure assessment, with the last-post baseline measurement being carried forward as the endpoint measurement. The primary efficacy assessment was to determine whether both valsartan and amlodipine monotherapy treatments contributed to the overall effect on change in mean sitting diastolic blood pressure observed with combination valsartan and amlodipine. The change in mean diastolic blood pressure from baseline to endpoint (primary efficacy variable) was analyzed using a two-way analysis of covariance model (ANCOVA) model with valsartan (each dose), amlodipine (each dose), and region as factors and baseline blood pressure as a covariate. The valsartan-by-amlodipine interaction was also included in the model. The test for each term (that is, valsartan, amlodipine, region, and valsartan-by-amlodipine interaction) was performed at a two-sided significance level of 0.05. It was considered that both monotherapy treatments contributed to the effect of the combination treatment if both tests for valsartan and amlodipine were statistically significant. The ANCOVAs were considered to be the primary global tests to assess the overall contribution of both valsartan and amlodipine monotherapies to the effect of the combination on the change in mean sitting diastolic blood pressure.

As a secondary assessment to quantify the add-on-effects for a given combination dose due to respective monotherapy doses a two-way ANCOVA model was used with treatment and region as two factors and baseline blood pressure as a covariate. The model also included a treatment-by-baseline interaction. All pairwise comparisons between treatments were made using this model. For a given combination dose, the hypotheses tested were that the combination dose was equal to each of its respective monotherapies and that the combination dose was not equal to each of its respective monotherapies. There were a number of secondary efficacy analyses including response surface analysis of the primary efficacy variable at endpoint, responder and control rate analyses, and Week 4 and 8 analyses of the primary efficacy variable. Standard and acceptable statistical methodologies were used to analyze the secondary efficacy outcomes.

The multi-factorial designs of both study 2201 and study 2307 were powered for the primary analyses of the global assessment of the treatment effect (that is, change in mean sitting diastolic blood pressure) on the primary efficacy variable (that is, mean sitting diastolic blood pressure), and also to provide response surface analyses across all doses in each study. The studies were not powered on the pairwise differences between individual monotherapy doses or between individual combinations. The sample size in both studies provided a power of greater than 90% for the primary efficacy assessment of determining whether both valsartan and amlodipine contributed to the overall effect of the combination on lowering blood pressure. In study 2201, a sample size of 110 completed patients per treatment group (1650 patients in total) was required to detect a difference of 3.5 mmHg in change from baseline in mean sitting diastolic blood pressure between two treatment groups with 90% power at a two-sided significance level of 0.05, assuming a standard deviation of 8 mmHg for each treatment

group. Assuming a drop-out rate of 10% from randomization to study completion, a sample size of 123 randomized patients per treatment group (1185 patients in total) was planned. In study 2307, a sample size of 150 completed patients per treatment group (900 patients in total) was required to detect a difference of 3.3 mmHg in change from baseline in mean sitting diastolic blood pressure between a combination treatment and its monotherapy components with a power of > 90% at a two-sided significance level of 0.05, assuming a standard deviation of 8 mmHg for each treatment group. Assuming a drop-out rate of 10% from randomization to study completion, a sample size of 188 randomized patients per treatment group (1128 patients in total) was planned. The final sample sizes in both studies were sufficient to satisfy the pre-specified power calculations.

Patient Demographics and Disposition

In study 2201, a total of 2478 patients were enrolled in the single-blind, run-in period. Of these 2478 patients, 1911 successfully completed the run-in period and were randomized, while 567 discontinued in the run-in period. The most common reasons for discontinuation in the run-in period were administrative problems (167 patients), patients condition no longer required the study drug (155 patients), and abnormal test results (83 patients). Of the 1911 patients randomized into one of the 15 treatment groups, 1738 (90.9%) completed the 8 week, double-blind period of the study and 173 (9.1%) discontinued (Table 4). The reasons for discontinuation in the double-blind treatment period were adverse events (27 [1.4%] patients), unsatisfactory therapeutic effect (57 [3.0%]), withdrawal of consent (45 [2.4%] patients) and other reasons (44 [2.3%] patients). The other reasons included abnormal laboratory values, abnormal test procedure results, subject's condition no longer required the study drug, protocol violation and administrative problems. Overall patient disposition and reasons for discontinuation in the double-blind treatment period in the four treatment groups of interest are summarised below in Table 5. The completion rate was lower in the placebo group than in the three active treatment groups. The discontinuation rates due to adverse events were similar for the four treatment groups of interest, while the discontinuation rate for unsatisfactory response was higher in the placebo group than in the three active treatment groups.

Table 4: Study 2201 – Number (%) of patients discontinued prematurely during double-blind phase by treatment group (randomized population).

Treatment Group	Total n (%)	Adverse Event(s) n (%)	Unsatisfactory Therapeutic Effect n (%)	Withdrawal of consent n (%)	Others[1] n (%)
Val/ Aml 320/5 mg	6 (4.7)	2 (1.6)	0 (0.0)	2 (1.6)	2 (1.6)
Val/ Aml 320/2.5 mg	8 (6.2)	1 (0.8)	3 (2.3)	3 (2.3)	1 (0.8)
Val/ Aml 160/5 mg	12 (9.4)	3 (2.4)	1 (0.8)	5 (3.9)	3 (2.4)
Val/ Aml 160/2.5 mg	15 (11.8)	1 (0.8)	4 (3.1)	0 (0.0)	10 (7.9)
Val/ Aml 80/5 mg	6 (4.7)	2 (1.6)	2 (1.6)	1 (0.8)	1 (0.8)
Val/ Aml 80/2.5 mg	6 (4.6)	1 (0.8)	2 (1.5)	3 (2.3)	0 (0.0)
Val/ Aml 40/5 mg	9 (7.2)	1 (0.8)	1 (0.8)	3 (2.4)	4 (3.2)
Val/ Aml 40/2.5 mg	7 (5.4)	3 (2.3)	0 (0.0)	2 (1.6)	2 (1.6)
Val 320 mg	12 (9.4)	3 (2.3)	3 (2.3)	4 (3.1)	2 (1.6)
Val 160 mg	10 (7.8)	0 (0.0)	5 (3.9)	4 (3.1)	1 (0.8)
Val 80 mg	11 (8.9)	1 (0.8)	3 (2.4)	3 (2.4)	4 (3.2)
Val 40 mg	12 (9.4)	0 (0.0)	7 (5.5)	2 (1.6)	3 (2.4)
Am 5 mg	15 (11.7)	2 (1.6)	4 (3.1)	6 (4.7)	3 (2.3)
Aml 2.5 mg	16 (12.7)	4 (3.2)	5 (4.0)	4 (3.2)	3 (2.4)
Placebo	28 (21.9)	3 (2.3)	17 (13.3)	3 (2.3)	5 (3.9)
Total	173 (9.1)	27 (1.4)	57 (3.0)	45 (2.4)	44 (2.3)

Source: PTT 7.1-1b
[1]Others include abnormal laboratory value(s), abnormal test procedure result(s), subject's condition no longer requires study drug, protocol violation, lost to follow-up, and administrative problems

Table 5: Study 2201 – Patient disposition and reasons for discontinuation (double-blind period) in the four treatment groups of interest.

Treatment Groups	Disposition			Reasons for Discontinuation in Double-Blind Period			
	Randomized	Completed	Discontinued	Adverse Events	Unsatisfactory Response	Consent Withdrawn	Other
Val/Aml 320/5 mg	127	121 (95.3%)	6 (4.7%)	2 (1.6%)	0 (0.0%)	2 (1.6%)	2 (1.6%)
Valsartan 320 mg	128	116 (92.2%)	12 (9.4%)	3 (2.3%)	3 (2.3%)	4 (3.1%)	3 (1.6%)
Amlodipine 5 mg	126	113 (88.3%)	15 (11.7%)	2 (1.6%)	4 (3.1%)	6 (4.7%)	3 (2.3%)
Placebo	128	100 (78.1%)	28 (21.9%)	3 (2.3%)	17 (13.3%)	3 (2.3%)	5 (3.9%)

For study 2201, the demographic characteristics of the four treatment groups of interest were similar with the mean age ranging from 53.7 to 56.8 years, the percentage of males ranging from 52.3% to 55.9%, and the most frequently represented racial group (Caucasian) ranging from 78.1% to 82.8%. The mean baseline sitting diastolic and systolic blood pressures were similar for the four treatment groups of interest ranging from 99.0 to 99.4 mmHg, and 151.6 to 154.6 mmHg, respectively. The mean duration of hypertension in the four treatment groups

of interest ranged from 7.0 to 8.7 years, with the majority of patients in each treatment group having a duration of at least 24 months.

In study 2307, a total of 1407 patients were enrolled in the single-blind run-in period. Of these 1407 patients, 1338 completed the run-in period and 1250 of these were randomized, while 67 patients were discontinued in the run-in period. The most common reasons for discontinuation in the run-in period were withdrawn consent (21 patients) and abnormal laboratory values (19 patients). Of the 1250 patients randomized into one of the 6 treatment groups, 1167 (93.4%) completed the 8-week, double-blind treatment period and 83 (6.6%) discontinued. The reasons for discontinuation in the double-blind treatment period were adverse events (29 [2.3%] patients), unsatisfactory therapeutic effect (17 [1.4%]), withdrawal of consent (16 [1.3%]) and other (21 [1.7%] patients). The other reasons included abnormal laboratory values, abnormal test procedure results, subject's condition no longer required study drug, protocol violation and administrative problems. Overall patient disposition and reasons for discontinuation in the double blind period in the four treatment groups of interest are summarised below in Table 6. The completion rate was lowest in the valsartan/amlodipine 320/10 mg group (91.4%) compared with the three other groups. The discontinuation rate due adverse events was highest in the amlodipine 10 mg group (3.9%) compared with the three other groups, while the discontinuation rate due to unsatisfactory therapeutic effect was highest in the valsartan 320 mg group (2.9%) compared with the three other groups.

Table 6: Study 2307 – Patient disposition and reasons for discontinuation (double-blind period) in the four treatment groups of interest.

	Disposition			Reasons for Discontinuation in Double-Blind Period			
Treatment Groups	Randomized	Completed	Discontinued	Adverse Events	Unsatisfactory Response	Consent Withdrawn	Other
Val/Aml 320/10 mg	210	192 (91.4%)	18 (8.6%)	5 (2.4%)	2 (1.0%)	4 (1.9%)	7 (3.3%)
Valsartan 320 mg	208	193 (92.8%)	15 (7.2%)	2 (1.0%)	6 (2.9%)	4 (1.9%)	3 (1.4%)
Amlodipine 10 mg	207	196 (94.7%)	11 (5.3%)	8 (3.9%)	0 (0.0%)	2 (1.0%)	1 (0.5%)
Placebo	209	195 (93.3%)	14 (6.7%)	5 (2.4%)	2 (1.0%)	2 (1.0%)	2 (1.0%)

For study 2307, the demographic characteristics of the four treatment groups of interest were generally similar with the mean age ranging from 55.4 to 58.0 years, the percentage of males ranging from 44.5% to 55.1%, and the most frequently represented racial group (Caucasian) ranging from 77.6% to 81.7%. The mean baseline sitting diastolic and systolic blood pressures were similar for the four treatment groups of interest ranging from 98.8 to 99.2 mmHg, and 156.2 to 157.5 mmHg, respectively. The mean duration of hypertension in the four treatment groups of interest ranged from 5.1 to 5.8 years, with the majority of patients in each treatment group having a duration of at least 24 months.

Primary Efficacy Results – MSDBP

In both study 2201 and study 2307, global assessment of the change from baseline in mean sitting diastolic blood pressure (MSDBP) at endpoint showed that both monotherapy treatments contributed to the overall reduction seen with combination treatment ($p<0.0001$

for both valsartan and amlodipine). In study 2201 (ITT population), all treatments produced statistically significant reductions in raw MSDBP from baseline to endpoint with the greatest reduction being seen with valsartan/amlodipine 320/5 mg (-15.74±0.554 mmHg [95% CI: -16.83, -14.64]; p<0.0001), and the smallest with placebo (-6.44±0.681 mmHg [95%CI: -7.78, -5.09]; p<0.001). Similarly, in study 2307 (ITT population) all treatments produced statistically significant reductions from baseline in raw MSDBP from baseline to endpoint with the greatest reduction being seen with valsartan/amlodipine 320/10 mg (-18.15±0.56 mmHg [95%CI: -19.249, -17.049]; p<0.0001], and the smallest with placebo (-8.25±0.60 mmHg [95%CI: -9.430, -7.063]; p<0.0001).

In study 2201 (ITT population), combination treatments were statistically significantly superior to their monotherapy components and placebo as regards MSDBP reduction at endpoint, with the only exceptions being [val/aml 320/2.5 mg versus val 320 mg] and [val/aml 40/2.5 mg versus aml 2.5 mg]. The maximum reduction in MSDBP with combination doses (after accounting for placebo) was generally achieved by 2 weeks of treatment. The least squares (LS) mean reductions in MSDBP at endpoint were 15.94 mmHg for valsartan/amlodipine 320/5 mg, 13.40 mmHg for valsartan 320 mg, 11.46 mmHg for amlodipine 5 mg, and 6.75 mmHg for placebo. The reduction in MSDBP was statistically significantly greater for valsartan/amlodipine 320/5 mg compared with valsartan 320 mg, amlodipine 5 mg, and placebo. The between-treatment comparisons for the four treatment groups of interest are summarised below in Table 7. Similar results to those observed in the ITT population were also seen in the PP population.

Table 7: Study 2201 - Between-treatment comparisons of MSDBP (mmHg) at endpoint (ITT population).

Comparison **	LS difference in change from baseline (SE)	95% CI in LSM difference	p-value
[Val/Aml 320/5 mg] versus [Val 320 mg]	-2.54 (0.917)	-4.34, -0.74	0.0057 *
[Val/Aml 320/5 mg] versus [Aml 5 mg]	-4.48 (0.920)	-6.28, -2.68	< 0.0001 *
[Val/Aml 320/5 mg] versus Placebo	-9.19 (0.920)	-10.99, -7.39	< 0.0001 *
[Val 320 mg] versus Placebo	-6.65 (0.916)	-8.44, -4.85	< 0.0001 *
[Aml 5 mg] versus Placebo	-4.71 (0.918)	-6.51, -2.91	< 0.0001 *

Note: Results from an ANCOVA model containing region, treatment, baseline and treatment by baseline. * Indicates significance at the 0.05 level. ** Number of patients in the ITT population for treatment groups: 126 [Val/Aml 320/5 mg]; 128 [Val 320 mg]; 128 [Aml 5 mg]; 127 [Placebo]. SE=standard error.

In study 2201, assessment of the effect of the various combinations on the MSDBP in subgroups (age, sex and race) was descriptive in nature. The results generally supported the effectiveness of the combinations in comparison with placebo, but the number of "Oriental" patients was too small to allow for definite conclusions to be made for this racial group. The mean reduction from baseline in MSDBP (versus placebo) for the valsartan/amlodipine 320/5 mg combination was 16.0 mmHg [n=100] (versus 6.3 mmHg [n=108]) in patients aged < 65, and 14.9 mmHg [n=26] (versus -7.0 mmHg [n=19]) in patients age≥ 65 years. The number of patients aged < 65 years was about four-fold higher than patients aged≥ 65 years.

In study 2307 (ITT population), both combination treatments were statistically significantly superior to their monotherapy components and placebo as regards MSDBP reduction at endpoint. The maximum reduction in MSDBP (after accounting for the placebo response) was seen after two weeks with valsartan/amlodipine 160/10 mg and after four weeks with valsartan/amlodipine 320 mg/10 mg (treatment initiated with 160/5 mg for the first week and then force titrated up to 320/10 mg). The reduction in MSDBP was statistically significantly greater for valsartan/amlodipine 320/10 mg compared with valsartan 320 mg, amlodipine 10 mg, and placebo. The between-treatment comparisons for the four treatment groups of interest are summarised below in Table 8. Similar results were observed in the PP population and in the analyses without inclusion of the treatment-by-baseline interaction.

Table 8: Study 2307 - Between-treatment comparisons of MSDBP (mmHg) at endpoint (ITT population).

Comparison **	LS difference in change from baseline (SE)	95% CI in LSM difference	p-value
[Val/Aml 320/10 mg] versus [Val 320 mg]	-5.33 (0.79)	-6.89, -3.78	< 0.0001 *
[Val/Aml 320/10mg] versus [Aml 10 mg]	-3.01 (0.79)	-4.57, -1.45	0.0002 *
[Val/Aml 320/10 mg] versus Placebo	-9.87 (0.79)	-11.42, -8.32	< 0.0001 *
[Val 320 mg] versus Placebo	-4.53 (0.79)	-6.08, -2.98	< 0.0001 *
[Aml 10 mg] versus Placebo	-6.86 (0.79)	-8.41, -5.30	< 0.0001 *

Note: Results from an ANCOVA model containing region, treatment, baseline and treatment by baseline. * Indicates significance at the 0.05 level. ** Number of patients in the ITT population for treatment groups: 208 [Val/Aml 320/10 mg]; 207 [Val 320 mg]; 206 [Aml 10 mg]; 209 [Placebo]. SE=standard error.

In study 2307, assessment of the effect of the various combinations on the MSDBP in subgroups (age, sex, and race) was descriptive in nature. The results generally supported the effectiveness of the combinations in comparison with placebo, but the number of Black patients was too small to allow for definite conclusions to be made for this racial group. The mean reduction from baseline in MSDBP (versus placebo) for the valsartan/amlodipine 320/10 mg combination was 18.1 mmHg [n=138] (versus 8.9 mmHg [n=147) in patients aged < 65, and 18.2 mmHg [n=70] (versus 6.6 mmHg [n=62]) in patients aged≥ 65 years. The mean reduction from baseline in MSDBP (versus placebo) for the valsartan/amlodipine 320/10 mg combination in males was 17.7 mmHg [n=112] (versus 6.9 mmHg [n=93]) compared with 18.7 mmHg (versus 9.3 mmHg [n=116]) in females.

Secondary Efficacy Results

Mean Sitting Systolic Blood Pressure

In both study 2201 and study 2307, global assessment of the change from baseline in the mean sitting systolic blood pressure (MSSBP) at endpoint showed that both monotherapy treatments contributed to the overall reduction seen with combination treatment ($p<0.0001$ for both valsartan and amlodipine). In study 2201, all treatments produced statistically significant reductions from baseline in raw MSSBP at endpoint with the greatest reduction being seeing with valsartan/amlodipine 320/5 mg (-22.37±1.054 mmHg [95% CI: -24.45, -20.28; $p<0.001$), and the smallest with placebo (-6.17±1.166 [95%CI: -8.48, -3.86]; $p<0.0001$). Similarly, in study 2307 all treatments produced statistically significant

reductions from baseline in the raw MSSBP at endpoint with the greatest reduction being seen with valsartan/amlodipine 320/10 mg (-26.95±0.93 mmHg [95%CI: -28.788, -25.111); p<0.001), and the smallest with placebo (-11.03±1.04 mmHg [95% CI: -13.087, -8.893]; p<0.0001).

In study 2201 (ITT population), combination treatments were statistically significantly superior (p<0.05) to their monotherapy components and placebo as regards MSSBP reduction at endpoint, with the only exceptions being [val/aml 320/2.5 mg versus val 320 mg] and [val/aml 160/2.5 versus val 160 mg]. The LS mean reductions in MSSBP were 22.74 mmHg for valsartan/amlodipine 320/5 mg, 15.68 mmHg for valsartan 320 mg, 15.07 mmHg for amlodipine 5 mg, and 6.74 mmHg for placebo. The reductions in MSSBP were statistically significantly greater (p<0.05) for valsartan/amlodipine 320/5 mg compared with valsartan 320 mg, amlodipine 5 mg, and placebo. The between-treatment comparisons for the four treatment groups of interest are summarised below in Table 9.

Table 9: Study 2201 - Between-treatment comparisons of MSSBP (mmHg) at endpoint (ITT population).

Comparison **	LS difference in change from baseline (SE)	95% CI in LSM difference	p-value
[Val/Aml 320/5 mg] versus [Val 320 mg]	-7.07 (1.465)	-9.94, -4.20	< 0.0001 *
[Val/Aml 320/5 mg] versus [Aml 5 mg]	-7.67 (1.457)	-10.53, -4.82	< 0.0001 *
[Val/Aml 320/5 mg] versus Placebo	-16.01 (1.463)	-18.88, -13.14	< 0.0001 *
[Val 320 mg] versus Placebo	-8.94 (1.465)	-11.8, -6.07	< 0.0001 *
[Aml 5 mg] versus Placebo	-8.33 (1.457)	-11.9, -5.48	< 0.0001 *

Note: Results from an ANCOVA model containing region, treatment, baseline and treatment by baseline. * Indicates significance at the 0.05 level.** Number of patients in the ITT population for treatment groups: 126 [Val/Aml 320/5 mg]; 128 [Val 320 mg]; 128 [Aml 5 mg]; 127 [Placebo].

In study 2307 (ITT population), both combination treatments were statistically significantly superior (p<0.05) to their monotherapy components and placebo as regards MSSBP reduction at endpoint. The LS mean reductions were 26.95 mmHg for valsartan/amlodipine 320/10 mg, 18.55 mmHg for valsartan 320 mg, 22.11 mmHg for amlodipine 10 mg, and 11.03 mmHg for placebo. The reductions in MSSBP were statistically significantly greater (p<0.05) for valsartan/amlodipine 320/10 mg compared with valsartan 320 mg, amlodipine 10 mg, and placebo. The between-treatment comparisons for the four treatment groups of interest are summarised below in Table 10.

Table 10: Study 2307 - Between-treatment comparisons of MSSBP (mmHg) at endpoint (ITT population).

Comparison **	LS difference in change from baseline (SE)	95% CI in LSM difference	p-value
[Val/Aml 320/10 mg] versus [Val 320 mg]	-8.52 (1.21)	-10.89, -6.15	< 0.0001 *
[Val/Aml 320/10 mg] versus [Aml 10 mg]	-4.25 (1.21)	-6.63, -1.88	0.0005 *
[Val/Aml 320/10 mg] versus Placebo	-15.49 (1.21)	-17.85, -13.12	< 0.0001 *
[Val 320 mg] versus Placebo	-6.96 (1.21)	-9.33, -4.94	< 0.0001 *
[Aml 10 mg] versus Placebo	-11.23 (1.21)	-13.61, -8.86	< 0.0001 *

Note: Results from an ANCOVA model containing region, treatment, baseline and treatment by baseline. * Indicates significance at the 0.05 level. ** Number of patients in the ITT population for treatment groups: 126 [Val/Aml 320/10 mg]; 128 [Val 320 mg]; 128 [Aml 10 mg]; 127 [Placebo].

Responder and Control Rates

In study 2201, the highest responder rates (MSDBP < 90 mmHg or $\geq$ 10 mmHg decrease compared with baseline) were achieved with valsartan/amlodipine 320/5 mg (91.3%) and the lowest with placebo (40.9%). A similar pattern was seen for the control rates (MSDBP < 90 mmHg) with the highest rate being observed with valsartan/amlodipine 320/5 mg (82.5%) and the lowest with placebo (33.9%) Responder rates at endpoint were statistically significantly superior ($p<0.05$) for all combination treatments compared with their monotherapy components and placebo, apart from [val/aml 320/2.5 mg versus val 320 mg], [val/aml 160/5 mg versus aml 5 mg], [val/aml 160/2.5 mg versus val 160 mg], [val/aml 40/2.5 mg versus val 40 mg], and [val/aml 40/2.5 mg versus aml 2.5 mg]. Control rates at endpoint were statistically significantly superior ($p<0.05$) for all combination treatments compared with their monotherapy components and placebo, apart from [val/aml 320/2.5 mg versus val 320 mg], [val/aml 160/5 mg versus aml 5 mg], [val/aml 80/5 mg versus aml 5 mg], [val/aml 40/5 mg versus aml 5 mg], [val/aml 40/2.5 mg versus val 40 mg], and [val/aml 40/2.5 mg versus aml 2.5 mg]. The results for responder and control rates for the four treatment groups of interest are summarised below in Table 11.

Table 11: Study 2201- Responder and control rates (ITT population).

Comparisons **	Responder Rate	p value	Control Rate	p value
[Val/Aml 320/5 mg] versus [Val 320 mg]	91.3 % versus 73.4%	0.0004 *	82.5% versus 67.2%	0.0052 *
[Val/Aml 320/5 mg] versus [Aml 5 mg]	91.3% versus 71.9%	0.0001 *	82.5% versus 64.8%	0.0016 *
[Val/Aml 320/5 mg] versus Placebo	91.3% versus 40.9%	< 0.0001 *	82.5% versus 33.9%	< 0.0001 *
[Val 320 mg] versus Placebo	73.4% versus 40.9%	< 0.0001 *	67.2% versus 33.9%	< 0.0001 *
[Aml 5 mg] versus Placebo	71.9% versus 40.9%	< 0.0001 *	64.8% versus 33.9%	< 0.0001 *

* Indicates significance at the 0.05 level. ** Number of patients in the ITT population for treatment groups: 126 [Val/Aml 320/5 mg]; 128 [Val 320 mg]; 128 [Aml 5 mg]; 127 [Placebo].

In study 2307, the highest responder rate was seen with valsartan/amlodipine 160 mg/10 mg (88.5%) followed by valsartan/amlodipine 320 mg/10 mg (87.5%), with the lowest occurring with placebo (49.3%). The responder and control rates for both combination treatments were statistically significantly superior ($p<0.05$) compared with corresponding valsartan monotherapy and placebo. However, neither of the combination treatments in study 2307 were statistically significantly superior compared with corresponding amlodipine monotherapy as regards the responder and control rates. The results for the responder and control rates for the four treatment groups of interest are summarised below in Table 12.

Table 12: Study 2307 - Responder and control rates (ITT population).

	Responder Rate	p value	Control Rate	p value
[Val/Aml 320/10 mg] versus [Val 320 mg]	87.5% versus 72.0%	0.0001 *	84.1% versus 63.8%	< 0.0001 *
[Val/Aml 320/10 mg] versus [Aml 10 mg]	87.5% versus 86.9%	0.8459	84.1% versus 80.1%	0.2793
[Val/Aml 320/10 mg] versus Placebo	87.5% versus 49.3%	< 0.0001 *	84.1% versus 42.6%	< 0.0001 *
[Val 320 mg] versus Placebo	72.0% versus 49.3%	< 0.0001 *	63.8% versus 42.6%	< 0.0001 *
[Aml 10 mg] versus Placebo	86.9% versus 49.3%	< 0.0001 *	80.1% versus 42.6%	< 0.0001 *

* Indicates significance at the 0.05 level. ** Number of patients in the ITT population for treatment groups: 126 [Val/Aml 320/10 mg]; 128 [Val 320 mg]; 128 [Aml 10 mg]; 127 [Placebo].

Comment

Both study 2201 and study 2307 satisfactorily established the efficacy of valsartan/amlodipine 320/5 mg and 320/10 mg combinations compared with placebo as regards the primary efficacy variable (MSDBP) and the secondary efficacy variables (MSSBP, responder rate, and control rate). In addition, both combinations were statistically significantly superior ($p<0.05$) compared with both of their respective monotherapies for the

primary efficacy variable (MSDBP) and the secondary efficacy variable (MSSBP). The valsartan/amlodipine 320/5 mg combination was statistically significantly superior ($p<0.05$) compared with both monotherapies as regards the secondary efficacy variables of responder and control rates. The valsartan/amlodipine 320/10 mg combination was statistically significantly superior ($p<0.05$) to valsartan 320 mg for both the secondary efficacy variables of responder and control rates, but not compared to amlodipine 10 mg for these two rates.

The placebo response rate for all primary and secondary efficacy variables was greater in study 2307 than in study 2201. The cross study comparison showed that placebo subtracted reductions in MSDBP (primary efficacy variable) were similar for the valsartan/amlodipine 320/5 mg and 320/10 mg combinations (9.19 mmHg and 9.87 mmHg, respectively). Similarly, the placebo subtracted reductions in MSSBP (secondary efficacy variable) were similar for both the valsartan/amlodipine 320/5 mg and 320/10 mg combinations (16.01 mmHg versus 15.49 mmHg). There were no direct comparisons between valsartan/amlodipine 320/5 mg and 320/10 mg combinations in the submitted efficacy studies.

Study 23071E – Long-Term Open-Label Extension Study

Objectives and Method

The primary objective of this 54-week open-label extension to study 2307 was to evaluate the safety, tolerability, and long-term efficacy of combination valsartan/amlodipine 320 mg/5 mg. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and in accordance with GCP and relevant legislation regulating clinical trials. All patients provided written informed consent.

The study enrolled patients from the 8-week, double-blind phase of study 2307 directly into the 54-week open-label phase. Enrollment into the extension phase was competitive and was limited to the first 400 (approximately) patients who successfully completed study 2307 and signed the informed consent for the extension. All patients who enrolled in the extension phase were guaranteed the opportunity to complete 6 months treatment, but only the first 150 (approximately) patients who successfully completed 6 months of treatment were eligible to continue the extension and were guaranteed the opportunity to complete 12 months treatment. The patient numbers were chosen to meet the CPMH/ICH/375/95 safety guidelines[9] for medicines intended to treat non-life threatening conditions which recommend exposure of at least 300 patients for 6 months and at least 100 patients for a minimum of 1 year.

The inclusion and exclusion criteria were the same as for study 2307 with two additions. These two additions were: (i) blood pressure had to be well controlled (that is, MSDBP < 90 mmHg and MSSBP < 140 mmHg; or MSDBP > 90 mmHg but ≤ 95 mmHg, and MSSBP > 140 mmHg but ≤ 150 mmHg at the investigator's discretion; and (ii) exclusion due to drug related serious adverse events in study 2307. Reasons for discontinuation in the extension phase included MSDBP ≥ 110 mmHg or MSSBP ≥ 180 mmHg at any time, and signs and

[9] "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions." The tripartite harmonised ICH guideline was finalised (*Step 4*) in October 1994. This document gives recommendations on the numbers of patients and duration of exposure for the safety evaluation of drugs intended for the long-term treatment of non-life-threatening conditions.

symptoms of hypotension with MSDBP < 60 mmHg and/or MSSBP < 100 mmHg at any time.

In the first 2 weeks of the extension phase patients took combination valsartan 160/2.5 mg OD (2 x 80 mg capsules of valsartan plus 1 x 2.5 mg tablet over-encapsulated of amlodipine). Following the initial 2-week treatment period, patients were force-titrated to combination valsartan/amlodipine 320/5 mg OD (2 x 80 mg capsules of valsartan plus 1 x 5 mg tablet over-encapsulated of amlodipine) for the remainder of the study. Visits in the extension stage were at Weeks 0, 2, 6, 15, 28, 41 and 54. Wherever possible, study assessments were made by the same person, at the same time of day, at each study visit.

Patient Population

A total of 1167 patients completed the 8-week, double-blind phase of study 2307, and of these 403 entered the open-label extension and 361 completed. Of the 361 patients who completed the extension, 214 completed at 6 months and 147 completed at 12 months. Of the 42 (10.4%) patients who discontinued, the reasons were adverse events (14 patients, 3.5%), withdrawn consent (12 patients 3.0%), administrative problems (8 patients, 2.0%), lost to follow-up (4 patients, 1.0%), protocol violation (2 patients, 0.5%), drug no longer required (1 patient, 0.2%), and unsatisfactory therapeutic effect (1 patient, 0.2%). Overall, the number of patients (n=396) who were titrated to valsartan/amlodipine 320/5 mg and exposed for 180 days or 362 days or longer to this combination was 310 and 115, respectively.

The mean±SD age of the 403 patients was 56.9±12.1 years (range: 19-85), and the majority of patients were < 65 years (n=288, 71.5%). There were 210 (49.9%) males and 202 (50.1%) females, and the majority of patients were Caucasian (n=380, 94.3%). The mean±SD height and weight were, respectively, 169.5±9.4 cm (range: 141-198) and 82.6±15.7 kg (range: 49-180). The mean±SD MSSBP, MSDBP, and pulse rate at baseline in study 2307 (that is, before 8-weeks of double-blind treatment) for the 403 patients were, respectively: 156.8±11.2 mmHg (range: 126.7 – 178.7); 98.7±97.7 mmHg (range: 95.0 – 109.7); and 74.2±8.4 beats per minute (bpm; range: 50-112).

Efficacy Results

The primary efficacy variable was the change from baseline (study 2307) in mean sitting diastolic blood pressure (MSDBP). The secondary efficacy variables were change from baseline (study 2307) in mean sitting systolic blood pressure, mean standing and sitting diastolic blood pressures, and mean sitting and standing pulse rate. The last non-missing measurement during the extension phase was carried forward as the endpoint extension phase measurement, and the results were summarised descriptively. The study showed that satisfactory reductions in MSDBP and MSSBP were maintained throughout the 54-week extension phase (Table 13, below).

Table 13: Summary statistics for change from baseline in MSDBP and MSSBP in the extension patients**.**

		Valsartan/Amlodipine 320/5 mg (N=403)					
		MSDBP (mmHg) Mean (SD)			MSSBP (mmHg) Mean (SD)		
Extension study week	n	Base	Post	Change	Base	Post	Change
Week 0	403	98.7 (3.3)	82.6 (6.3)	-16.1 (6.5)	156.8 (11.2)	132.8 (9.4)	-24.0 (11.4)
Week 2	402	98.7 (3.3)	83.1 (7.1)	-15.6 (6.9)	156.7 (11.2)	134.0 (11.2)	-22.7 (12.2)
Week 6	395	98.7 (3.3)	81.2 (6.6)	-17.5 (6.8)	156.7 (11.2)	130.9 (11.3)	-25.8 (12.6)
Week 15	389	98.7 (3.3)	81.1 (6.6)	-17.6 (6.6)	156.7 (11.1)	130.9 (11.1)	-25.8 (12.5)
Week 28	376	98.8 (3.4)	81.6 (6.8)	-17.2 (6.8)	156.9 (11.1)	131.8 (10.7)	-25.1 (12.9)
Week 41	155	98.7 (3.1)	82.7 (7.7)	-16.0 (7.7)	156.9 (11.0)	133.4 (11.7)	-23.4 (13.1)
Week 54	148	98.7 (3.1)	81.3 (7.1)	-17.4 (6.8)	156.9 (11.0)	132.6 (11.6)	-24.3 (12.2)
Endpoint	402	98.7 (3.3)	81.7 (7.3)	-17.0 (7.3)	156.7 (11.2)	132.5 (11.8)	-24.2 (13.0)

Base=Core-baseline, Change=Post - Base.
Endpoint is the value at Week 54 or LOCF value.
At each time point, only patients with a value at both Baseline and this time point are included.

The summary statistics for the MSDBP and MSSBP at endpoint for the subgroups (< 65 and ≥ 65 years; male and female) showed that valsartan/amlodipine 320/5 mg satisfactorily maintained blood pressure over the 54-week extension phase in both subgroups. Blood pressure was also satisfactorily maintained in the Caucasian subgroup, but patient numbers were too small in other racial groups to allow meaningful conclusions to be made. The study also showed that satisfactory reductions in mean standing diastolic and systolic blood pressure were maintained throughout the extension phase with the respective endpoint reductions being 15.9 mmHg and 23.5 mmHg from baseline in study 2307. At all visits in the extension phase the standing diastolic and systolic blood pressures were <90 mmHg and < 140 mmHg, respectively. Only small, clinically insignificant changes in sitting and standing pulse rate were observed throughout the extension phase.

Comment

The open-label, 54-week, extension study showed that the valsartan/amlodipine 320/5 mg combination satisfactorily maintained long-term blood pressure reduction. However, there was no placebo-controlled treatment group which limits interpretation of the data.

Safety

Study 2201 and Study 2307 – Short-Term (8-week, placebo-controlled)

Overview

These two, randomized, placebo-controlled studies of 8-weeks, double-blind treatment included a total of 3155 patients of whom 1437 received combination valsartan/amlodipine (40-320/2.5-10 mg). There were 210 patients treated with valsartan/amlodipine 320/10 mg and 127 patients treated with valsartan/amlodipine 320/5 mg. Overall, more than 90% of patients completed the studies with the highest rate of discontinuations being seen in the placebo group, primarily due to unsatisfactory therapeutic response.

In *study 2201*, the mean±SD exposure to valsartan/amlodipine 320/5 mg (n=127) was 55.3±7.7 days (range: 7-69), compared with 54.4±9.5 days (range: 6-70) for valsartan 320 mg (n=128), 53.9±10.0 days (range: 14-68) for amlodipine 5 mg (n=126), and 48.6±17.0 days (range 1-83) for placebo (n=128).

In *study 2307*, the mean±SD exposure to valsartan/amlodipine 320/10 mg (n=210) was 55.1±11.8 days (range: 2-121), compared with 54.7±10.9 days (range: 7-120) for valsartan 320 mg (n=208), 55.9±11.0 days (range: 7-130 days) for amlodipine 10 mg (n=207), and 54.9±11.7 days (range: 4-119) for placebo.

Adverse Events (AEs)

In *study 2201*, the overall AE rate (at least one new or worsened AE after randomization) was 48.6% (n=925) in the total safety population (n=1905). The highest overall rate of AEs occurred in the valsartan/amlodipine 160/5 mg group (54.8%; 69/127). The overall rate of AEs in the valsartan/amlodipine 320/5 mg group was 46.5% (59/127), compared with 49.2% (63/128) for valsartan 320 mg, 50.8% (65/128) for amlodipine 5 mg and 50.0% (64/128) for placebo. The most frequently reported individual adverse events (≥ 2%) reported in the valsartan/amlodipine 320/5 mg group were headache, dizziness, diarrhoea, nasopharyngitis, bronchitis, dyspepsia, fatigue, limb injury and peripheral oedema. The rates for these 9 AEs in the treatments of interest are summarised below in Table 14.

Table 14: Study 2201 - Percent (%) of patients with most frequently reported AES (≥ 2% in the valsartan/amlodipine 320/5 mg group) in the safety population.

Adverse Event	V/A 320/5 mg n=127	All V/A n=1018	Val 320 mg n=128	Aml 5 mg n=128	Placebo n=128
Headache	5.5%	5.3%	7.8%	8.6%	9.4%
Dizziness	3.9%	2.5%	6.3%	2.9%	2.3%
Diarrhoea	3.1%	2.5%	2.3%	1.6%	2.3%
Nasopharyngitis	3.1%	5.2%	7.8%	3.9%	4.7%
Bronchitis	2.4%	1.8%	1.6%	0.0%	0.8%
Dyspepsia	2.4%	1.1%	1.6%	1.6%	0.8%
Fatigue	2.4%	1.7%	2.3%	3.1%	2.3%
Limb Injury	2.4%	0.3%	0.0%	0.0%	0.8%
Peripheral oedema	2.4%	3.2%	2.3%	3.1%	6.3%

V/A = valsartan/amlodipine; All V/A = all patients in the valsartan/amlodipine combinations (40-325/2.5-5 mg); Val = Valsartan; Aml = Amlodipine.

In *study 2201*, the incidence of any oedema (peripheral, eyelid, oedema, periorbital, pitting and swollen tongue) with valsartan/amlodipine 320/5 mg was 2.4% compared with 3.9% with valsartan 320 mg, 3.1% with amlodipine 5 mg, and 7.0% with placebo. The incidence of any oedema was particularly high in the placebo treated group. The incidence of patients with AEs suspected to be drug related were 11.0% (n=14) with valsartan/amlodipine 320/5 mg, 9.3% (n=95) with valsartan/amlodipine all combinations, 7.5% (n=38) with valsartan monotherapy all strengths, 11.9% (n=30) with amlodipine both strengths, and 10.9% (n=14) with placebo. In the total population (n=1905), the most commonly occurring AEs (≥ 1%)

suspected of being treatment related was peripheral oedema (1.8%), followed by headache (1.3%). In the valsartan/amlodipine 320/5 mg group, the most commonly occurring AEs (≥ 1%) suspected of being drug-related were peripheral oedema, headache, dizziness and fatigue, each of which occurred in 2 (1.6%) patients. There was no evidence of dose dependency for any of the most frequently reported AEs. Peripheral oedema occurred more frequently with amlodipine 2.5 mg (8%) than with amlodipine 5 mg (3.1%).

In *study 2307*, one or more AEs occurred in 33.2% of patients (n=415) in the total safety population (n=1250). The highest overall rate of AEs occurred in the valsartan/amlodipine 160/10 mg group (39.2%; 82/209). The AE rate in the valsartan/amlodipine 320/10 mg group was 32.4% (68/210), which compared with 28.4% (59/208) for valsartan 320 mg, 38.2% (79/207) for amlodipine 10 mg and 31.1% (65/209) for placebo. The most frequently reported individual AEs (≥ 1%) in the valsartan/amlodipine 320/10 mg group were peripheral oedema, nasopharyngitis, upper respiratory tract infection, dizziness, asthenia, fatigue, arthralgia, back pain, bronchitis, constipation, gastroenteritis, headache, hot flush, insomnia, palpitations and vertigo. The rates for these 17 AEs for all treatments are summarised below in Table 15.

Table 15: Study 2307 - AEs by preferred term and treatments group (≥ 1% in the valsartan/amlodipine 320/10 mg group) in the safety population.

Preferred term	Val/Aml 320/10 mg N=210 n (%)	Val/Aml 160/10 mg N=209 n (%)	Val 320 mg N=208 n (%)	Val 160 mg N=207 n (%)	Aml 10 mg N=207 n (%)	Placebo N=209 n (%)
Any adverse experience	68 (32.4)	82 (39.2)	59 (28.4)	62 (30.0)	79 (38.2)	65 (31.1)
Edema peripheral	20 (9.5)	24 (11.5)	0 (0.0)	2 (1.0)	26 (12.6)	2 (1.0)
Nasopharyngitis	5 (2.4)	4 (1.9)	1 (0.5)	6 (2.9)	4 (1.9)	0 (0.0)
Upper respiratory tract infection	5 (2.4)	1 (0.5)	1 (0.5)	2 (1.0)	2 (1.0)	4 (1.9)
Dizziness	4 (1.9)	1 (0.5)	4 (1.9)	2 (1.0)	1 (0.5)	0 (0.0)
Asthenia	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	1 (0.5)
Fatigue	3 (1.4)	0 (0.0)	1 (0.5)	0 (0.0)	4 (1.9)	2 (1.0)
Arthralgia	2 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)	1 (0.5)	1 (0.5)
Back pain	2 (1.0)	1 (0.5)	2 (1.0)	2 (1.0)	4 (1.9)	2 (1.0)
Bronchitis	2 (1.0)	1 (0.5)	2 (1.0)	3 (1.4)	4 (1.9)	3 (1.4)
Constipation	2 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	3 (1.4)	0 (0.0)
Gastroenteritis	2 (1.0)	1 (0.5)	3 (1.4)	0 (0.0)	1 (0.5)	2 (1.0)
Headache	2 (1.0)	6 (2.9)	5 (2.4)	9 (4.3)	11 (5.3)	8 (3.8)
Hot flush	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	2 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)
Palpitations	2 (1.0)	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	2 (1.0)
Vertigo	2 (1.0)	4 (1.9)	3 (1.4)	3 (1.4)	0 (0.0)	0 (0.0)

- Preferred terms are sorted in descending frequency, as reported in the Val/Aml 320/10 mg column.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE preferred term for that treatment.

In *study 2307*, the incidence of any oedema was 6.3% (n=79) in the safety total population. The incidence of any oedema was 9.5% (n=20) with valsartan/amlodipine 320/10 mg, 0% with valsartan 320 mg, 13.5% (n=28) with amlodipine 10 mg (the highest incidence of all treatments) and 1.4% (n=3) with placebo. There was one case of serious acute pulmonary oedema which occurred in the placebo group and resulted in discontinuation. The only other report of severe oedema was peripheral oedema occurring with valsartan/amlodipine 160/10 mg. Peripheral oedema resulted in discontinuations in 12 patients (1 with valsartan/amlodipine 320/10 mg, 5 with valsartan/amlodipine 160/10 mg, and 6 with amlodipine 10 mg).

In *study 2307*, 142 (11.4%) patients experienced an AE suspected to be drug related. Suspected drug related AEs were reported in 29 (13.8%) patients treated with valsartan/amlodipine 320/10 mg, compared with 12 (5.8%) with valsartan 320 mg, 35 (16.9%) with amlodipine 10 mg, and 13 (6.2%) with placebo. In the valsartan 320/10 mg group the most frequently occurring AEs (≥ 1%) suspected to be drug related were peripheral oedema (9.0%; n=19), dizziness (1.4%; n=3), asthenia (1.0%; n=2), hot flush (1.0%; n=2), and vertigo (1.0%; n=2).

Deaths, Other Serious Adverse Events (SAEs), and Other Significant Adverse Events.

In *study 2201*, no deaths occurred during the study. However, there was one death in a patient discontinued in the single-blind placebo run-in phase. In the total population, 15 (0.8%) patients reported at least one SAE, 28 (1.5%) discontinued due to an AE (that is, other significant adverse events), and 7 (0.4%) discontinued due to a SAE in the double-blind treatment phase. No more than 2 patients (≤1.6%) in any individual treatment group experienced one or more SAEs, and the events were not clustered in any particular organ system. In the valsartan/amlodipine 320/5 mg group, one patient experienced a SAE (kidney stones), while two patients experienced significant other AEs resulting in discontinuation (1 x nocturia and palpitations; 1 x muscle twitch). Discontinuations due to AEs occurred at similar frequencies across all treatment groups. Headache was the most frequent AE resulting in discontinuation (6 patients; 0.3%) followed by hypertensive crisis (3 patients; 0.2%) and palpitations (2 patients; 0.2%). Two patients discontinued due to elevated glycosylated haemoglobin levels. There was only one SAE considered to be drug related and this event resulted in discontinuation (severe hypertensive crisis in a patient in the valsartan/amlodipine 80/5 mg group). The results for deaths, serious AEs and discontinuations due to SAEs or AEs are summarised below in Table 16.

Table 16: Study 2201 - Number (%) of patients who died, had SAEs, or discontinued due to AEs or SAEs in the safety population.

	n	Deaths n (%)	SAEs n (%)	Disc AEs n (%)	Disc SAEs n (%)
V/A 320/5 mg	127	0	1 (0.8)	2 (1.6)	0
All V/A	1018	0	7 (0.7)	15 (1.5)	5 (0.5)
Val 320 mg	128	0	1 (0.8)	3 (2.3)	0
Aml 5 mg	128	0	1 (0.8)	2 (1.6)	0
Placebo	128	0	1 (0.8)	3(2.3)	0

V/A = valsartan/amlodipine; All V/A = all patients in the valsartan/amlodipine combinations (40-325/2.5-5 mg); Val = Valsartan; Aml = Amlodipine; Disc AEs = Discontinued due to adverse events; Disc SAEs = Discontinued due to SAEs.

In *study 2307*, no deaths occurred during the study. However, there was one death in a patient discontinued in the single-blind placebo run-in phase. In the total population (n=1250), there were 9 (0.7%) SAEs, 29 (2.3%) AEs resulting in discontinuation, and 5 (0.4%) SAEs resulting in discontinuation in the double-blind treatment phase. No more than 3 patients (≤ 1.4%) in any treatment group experienced one or more SAEs, and the events were no clustered in any particular organ system. In the valsartan/amlodipine 320/10 mg group, two patients experienced a SAE (1 x prostate cancer; 1 x pulmonary embolism) and two patients

experienced other clinically significant AEs resulting in discontinuation (1 x worsening of vertigo; 1 x worsening of lower leg oedema). The results for deaths, serious AEs, and discontinuations due to SAEs or AEs are summarised below in Table 17.

Table 17: Study 2307 - Number (%) of patients who died, had SAEs, or discontinued due to AEs or SAEs in the safety population.

	n	Deaths n (%)	SAEs n (%)	Disc AEs n (%)	Disc SAEs n (%)
V/A 320/10 mg	210	0	2 (1.0)	5 (2.4)	2 (1.0)
V/A 160/10 mg	209	0	1 (0.5)	7 (3.3)	0
Val 320 mg	208	0	1 (0.5)	2 (1.0)	0
Val 160 mg	207	0	1 (0.5)	2 (1.0)	0
Aml 10 mg	207	0	1 (0.5)	8 (3.9)	0
Placebo	209	0	3 (1.9)	5 (2.4)	3 (1.4)

V/A = valsartan/amlodipine; All V/A = all patients in the valsartan/amlodipine combinations (40-325/2.5-5 mg); Val = Valsartan; Aml = Amlodipine; Disc AEs = Discontinued due to adverse events; Disc SAEs = Discontinued due to SAEs.

Laboratory Values

In *study 2201*, mean and median changes from baseline at endpoint in *haematology parameters* were clinically unremarkable in all treatment groups. In the valsartan/amlodipine 320/5 mg group, no patients experienced a > 50% increase in red blood cell (RBC) count, one patient experienced a > 20% decrease in RBC count, no patients experienced a > 50% increase or decrease in white blood cell (WBC) count, one patient experienced a > 75% increase in platelet count and no patients experienced a > 50% decrease in platelet count. As regards *biochemistry parameters*, mean and median changes from baseline were generally clinically unremarkable in all treatment groups with the exception of unexplainable increases in creatinine kinase (CK). In the valsartan/amlodipine 320/5 mg group, the number of patients (treatment versus placebo) with values outside the pre-specified changes (%) from baseline to endpoint in biochemical parameters were: > 5% decrease in sodium (1 [0.8%] versus 1 [0.9%]); > 20% increase in potassium (4 [3.3%] versus 2 [1.7%]); > 50% increase in glucose (1 [0.8%] versus 1 [0.9%]); > 100% increase in bilirubin (5 [4.2%] versus 2 [1.7%]); > 50% increase in blood urea nitrogen (BUN) (2 [1.6%] versus 5 [4.3%]); > 10% increase in calcium (3 [2.5%] versus 1 [0.9%]); and > 10% decrease in calcium (2 [1.6%] versus 0% placebo). There were no reported urinalysis results suggesting that baseline and endpoint results were not collected and/or not reported.

In *study 2307*, mean and median changes from baseline at endpoint in *haematology parameters* were clinically unremarkable in all treatment groups. In the valsartan/amlodipine 320/10 mg group, the only parameter which changed more frequently compared with placebo was > 50% decrease in WBC count of 2.0% (4/196) (versus 1.0% [2/202], placebo). As regards the *biochemistry parameters*, mean and median changes from baseline at endpoint

were generally clinically unremarkable. In the valsartan/amlodipine 320/10 mg group, the parameters which changed more frequently compared with placebo were: > 50% increase in BUN of 5.0% (10/201) (versus 4.9% [10/205], placebo); > 10% increase in calcium of 2.5% (5/201) (versus 2.0% [4/205], placebo); > 50% decrease in glucose of 1.0% (2/199) (versus 0% for placebo); > 20% decrease in potassium of 3.0% (6/200) (versus 1.0% [2/205], placebo); > 150% increase in alanine transaminase (ALT) of 2.0% (4/200) (versus 0.5% [1/205], placebo); > 5% decrease in sodium of 1.0% (2/201) (versus 1.5% [3/203], placebo); and > 100% increase in bilirubin of 3.0% (6/197) (versus 1.5% [3/203], placebo). There were no reported urinalysis results suggesting that baseline and endpoint results were not collected and/or not reported.

Orthostatic Hypotension

In *study 2201*, orthostatic hypertension (that is, ≥ 20 mmHg decrease in systolic blood pressure or ≥ 10 mmHg decrease in diastolic blood pressure from sitting to standing) at any post-baseline visit was recorded in 13 (10.3%) valsartan/amlodipine 320/5 mg treated patients compared with 87 (8.6%) for all valsartan/amlodipine combinations, 17 (13.3%) for valsartan 320 mg, 13 (10.2%) for amlodipine 5 mg, and 14 (11.0%) for placebo. There was no dose response for orthostatic hypotension in the valsartan/amlodipine combinations with the percentage of patients with this event being greatest with the 80/2.5 mg combination.

In *study 2307*, orthostatic hypotension at any post-baseline visit was recorded in 18 (8.7%) valsartan/amlodipine 320/10 mg treated patients, compared with 19 (9.2%) for valsartan 320 mg, 21 (10.2%) for amlodipine 10 mg, and 11 (5.3%) for placebo. There was no response for orthostatic hypotension for valsartan/amlodipine 320/10 mg (8.7%) and valsartan 160/10 mg (10.0%), and this event was most commonly observed with amlodipine 10 mg (10.2%).

Study 23071E – Long-Term (54-week) Open-Label Extension Study

Exposure

This study was an open-label 54-week extension to *study 2307* in patients with uncomplicated essential hypertension of mild to moderate intensity. In the extension study, the mean±SD duration of exposure to valsartan/amlodipine 320/5 mg OD (n=396) was 245.6±95.8 days (range: 8-378). Of the 396 patients exposed to 320/5 mg, 154 (38.9%) were exposed for 180 to < 271 days, 41 (10.4%) for 271 to < 362 days, and 115 (29.0%) for ≥ 362 days. Overall, 310 patients were exposed to 320/5 mg for approximately 6 months or longer and 115 for approximately 12 months or longer.

Discontinuations

Of the 403 patients entering the extension phase, 361 completed (89.6%) and 42 (10.4%) discontinued. The reasons for patients discontinuing were: AEs 3.5% (14); SAEs 1.0% (4); subject withdrew consent 3.0% (12); administrative problems 2.0% (8); lost to follow-up 1.0% (4); protocol violation 0.5% (2); subject's condition no longer requires study drug 0.2% (1); and unsatisfactory therapeutic effect 0.2% (1).

Adverse Events

Adverse events occurred in 41.4% (167/403) of the total population. The most frequently affected (≥ 5%) primary system organ classes in the 403 patients were infections and infestations (18.1%), musculoskeletal and connective tissue disorders (12.4%), nervous system disorders (9.2%), and gastrointestinal disorders (7.7%). The most commonly affected organ systems were infections/infestations (18.1%), musculoskeletal and connective tissue (12.4%) and nervous system disorders (9.9%).The most frequently reported AEs were bronchitis (4.5%), back pain (2.5%), nasopharyngitis (2.5%) and sinusitis (2.5%). All other

AEs occurred with a frequency of≤ 2.0%. AEs possibly associated with low blood pressure included hypotension (0.5%), syncope (0.2%), and dizziness (0.2%). There were no AE reports of postural dizziness, lightheadedness or orthostatic hypotension. AEs with a frequency of≥ 2% are summarised below in Table 18.

Table 18: Study 2307 – Number (%) of patients with AEs reported with a frequency ≥ of 2%.

Adverse events (preferred term)	Valsartan/Amlodipine 320/5 mg N=403 n (%)
Any adverse experience	167 (41.4)
Bronchitis	18 (4.5)
Back pain	10 (2.5)
Nasopharyngitis	10 (2.5)
Sinusitis	9 (2.2)
Arthralgia	8 (2.0)
Cervicobrachial syndrome	8 (2.0)
Sciatica	8 (2.0)
Vertigo	8 (2.0)

The incidence of oedema of all types was 2.2% (9/403), consisting of peripheral oedema 1.2% (n=5), oedema 0.7% (n=3), and eyelid oedema 0.2% (n=1). There were no cases of serious or severe oedema, and no patients were discontinued due to oedema. The incidence of AEs suspected of being drug related was 4.7% (19/403), and the only AEs suspected of being drug related and occurring in at least two patients were peripheral oedema (n=4; 1.0%), erectile dysfunction (n=2; 0.5%), hypotension (n=2; 0.5%), and oedema (n=2; 0.5%). Only 2.5% of patients were reported to have severe AEs.

Deaths, Other Serious Adverse Events (SAEs), and Other Significant Adverse Events.

During the 54-week extension there were no deaths, 17 (4.2%) SAEs, 13 (3.2%) AEs leading to discontinuation (that is, other significant AEs), and 4 (1.0%) SAEs leading to discontinuation. There was no particular pattern or clustering of events according to system organ class or preferred term for the reported SAEs. The SAEs according to preferred term were epigastric herniation, umbilical hernia, urinary incontinence, kidney stone, urosepsis due to prostate hypertrophy, acute pancreatitis, prostatic cancer, depression, worsening of headache, cerebral "apoplexy", fracture of vertebral body and serious back pain, fracture of the left arm, left hiparthrosis, worsening of arterial occlusive disease, hypertensive crisis, angina pectoris and allergic skin reaction.

The SAEs in the 4 (1.0%) patients who discontinued were depression (x1), allergic dermatitis (x1), cerebrovascular accident (x1) and hypertensive crisis (x1). The AEs in the 13 (3.2%) patients who discontinued were depression (x2), erectile dysfunction (x2), hypertensive crisis (x2), arrhythmia supraventricular (x1), atrial fibrillation (x1), cardiovascular disorder (x1), cerebrovascular accident (x1), dermatitis allergic (x1), dizziness (x1), hypotension (x1), and thrombosis (x1).

Laboratory Values

Mean and median changes from baseline at endpoint for the *haematology parameters* were clinically unremarkable, as were the shift analyses at baseline and all post-baseline visits. The incidence of patients with haematology values exceeding specified percentage changes from baseline was≤ 0.8% (that is, ≤ 3 patients) for all parameters, apart from > 50% increase in

total WBC count which occurred in 6.4% (25) of patients. The increase in the WBC count is consistent with the frequently reported AEs of bronchitis, nasopharyngitis, and sinusitis occurring in the study. The mean and median changes from baseline at endpoint for the *biochemistry parameters* were clinically unremarkable, as were the shift analyses at baseline and all post-baseline visits. The highest incidence of patients (n=403) with biochemistry values exceeding specified percentage changes from baseline occurred for > 50% increases in BUN (10.9%), followed by > 20% increase in potassium (9.4%), > 10% increase in calcium (7.6%), > 100% increase in total bilirubin (3.3%), > 20 % decrease in potassium (2.8%), > 150% increase in ALT (2.8%), > 50% increase in uric acid (1.8%), > 150% in AST (1.5%), > 10% decrease in calcium (1.3%), > 50% increase in creatinine (1.3%), and > 300% increase in CK (1.0%). Percentage changes in all other measured biochemistry parameters were < 1.0% (that is,< 4 patients). There were no reported urinalysis results suggesting that baseline and endpoint results were not collected and/or not reported.

Orthostatic Hypotension

The incidence of patients with orthostatic hypotension at endpoint was 1.3% (5/392), and the incidence at any visit was 5.5% (22/402). The incidence of orthostatic hypotension remained relatively low at all visits (0.7% to 3.2%)

Post-Marketing Experience

There were no post-marketing data relating to valsartan/amlodipine 320/5 mg and 320/10 mg combination tablets.

Clinical Evaluator's Conclusions and Recommendations

a. The sponsor proposes registration of Exforge (Ejocia) valsartan/amlodipine 320/5 mg and 320/10 mg fixed combination tablets as replacement therapy in patients whose blood pressure is adequately controlled on amlodipine and valsartan used as individual therapies. The submission included no clinical efficacy and safety studies in which patients stabilized on valsartan (320 mg) and amlodipine (5 mg or 10 mg) were switched to the corresponding fixed combinations (320/5 mg or 320/10 mg). In both *study 2201* and *study 2307*, the clinical efficacy and safety of combination treatments were compared with their individual components and placebo in a parallel group design.

b. Data from pharmacokinetic *study 2310*, showed that valsartan 320 mg (2 x 160 mg capsules) and amlodipine 5 mg (over-encapsulated tablet) administered together and valsartan/amlodipine 320/5 mg fixed combination tablets (FMI) were bioequivalent as regards the C_{max} and AUC of both valsartan and amlodipine. The individual valsartan 160 mg capsules and amlodipine 5 mg tablets used in *study 2310* were not Australian approved products. However, the sponsor claims that the valsartan capsules used in the Exforge clinical study program have been shown in previous submissions to be bioequivalent to Australian registered Diovan (valsartan) products. In addition, the sponsor states that although it has not undertaken a bioequivalence study comparing the US Norvasc (amlodipine) 5 mg tablet used in *study 2310* with the corresponding Australian approved Norvasc (amlodipine) 5 mg tablet, it is reasonable to assume that the bioavailability of the two products is unlikely to be significantly different. *Study 2310* has been evaluated by the TGA previously and its relevance to Australian clinical practice has been accepted by the TGA following advice from the ADEC (255^{th} Meeting). It is considered that the available pharmacokinetic evidence indicates that Australian patients stabilized on combination treatment with valsartan 320 mg tablets and amlodipine 5 mg tablets can be safely switched to treatment with the proposed valsartan/amlodipine 320/5 mg fixed combination tablet.

c. The submission included no bioequivalence study comparing valsartan/amlodipine 320/10 mg fixed combination tablets as proposed for registration with valsartan 320 mg tablets (or capsules) and amlodipine 10 mg tablets. The sponsor provided a justification for not providing such a study. The clinical aspects of this justification are considered to be acceptable and the biopharmaceutical chemistry aspects appear to be reasonable. However, definitive acceptance of the biopharmaceutical aspects of the justification is primarily a matter for the quality evaluator. In the original submission, the PSC accepted the sponsor's justification for not submitting bioequivalence studies for the valsartan/amlodipine 80/5 mg and 160/5 mg combinations (PSC Minutes, 113th Meeting). These justifications appear to be similar in nature to that submitted for the valsartan 320/10 mg combination. There were no pharmacokinetic studies investigating the effect of food on the valsartan/amlodipine 320/5 mg or 320/10 mg combinations. However, the currently approved Exforge (Ejocia) PI states that the bioavailability of amlodipine is unaffected by food, and that the "[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".

d. The submission included two, high-quality, multi-national, randomized, placebo-controlled, double-blind, short-term, clinical efficacy and safety studies [2201; 2307]. Based on these two studies it is concluded that the short-term (8-week) efficacy of both valsartan 320/5 mg and valsartan 320/10 mg combinations has been satisfactorily demonstrated. In *study 2201,* valsartan 320/5 mg reduced the mean sitting diastolic blood pressure (primary efficacy variable) to a significantly greater extent than valsartan 320 mg, amlodipine 5 mg, and placebo. In addition, valsartan 320/5 mg significantly reduced the mean sitting systolic blood pressure (a secondary efficacy endpoint) and significantly increased the responder and control rates (secondary efficacy endpoints) compared with both of its components and placebo. In *study 2307,* valsartan 320/10 mg reduced the mean sitting diastolic blood pressure (primary efficacy variable) to a significantly greater extent than valsartan 320 mg, amlodipine 10 mg, and placebo. In addition, valsartan 320/10 mg significantly reduced the mean sitting systolic blood pressure (a secondary efficacy endpoint) compared with both of its components and placebo, and significantly increased the responder and control rates rate (secondary efficacy variables) compared with valsartan 320 mg and placebo but not for amlodipine 10 mg. No studies were submitted investigating withdrawal or rebound effects on the efficacy of the two combinations.

e. It is considered that the short-term (8-week) safety of valsartan 320/5 mg and valsartan 320/10 mg combinations has been satisfactorily established. No new or unexpected safety issues appeared with the combinations in either *study 2201* (320/5 mg combination) or *study 2307* (320/10 mg combination). In both studies, most AEs were considered to be mild to moderate in intensity, and not suspected of being drug related. In *study 2201*, the incidence of AEs in patients in the treatment groups of interest was 46.5% with valsartan/amlodipine 320/5 mg, 49.2% with valsartan 320 mg, 50.8% for amlodipine 5 mg, 50.0% for placebo, and 48.6% in all valsartan/amlodipine combination groups. Overall, in the total safety population the most frequently reported AE was headache (6.3%), and this AE was also the most frequently reported AE in the valsartan/amlodipine 320/5 mg group (5.5%). Other frequently AEs occurring in the total safety population (versus valsartan/amlodipine 320/5 mg) were nasopharyngitis (5.3% versus 3.1%), peripheral oedema (3.8% versus 2.4%), upper respiratory tract infection (3.0% versus < 2.0%), dizziness (2.6% versus 3.9%), and diarrhoea (2.2% versus 3.1%). Orthostatic hypotension was reported in 10.3% of valsartan/amlodipine 320/5 mg treated patients, 13.3% with valsartan 320 mg, 10.2% with amlodipine 5 mg, and 11.0% with placebo. In *study 2307*, the incidence of AEs in patients in all treatment groups was 32.4% with valsartan/amlodipine 320/10 mg, 39.2% with valsartan amlodipine 160/10

mg, 28.4% with valsartan 320 mg, 30.0% with valsartan 160 mg, 38.2% with amlodipine 10 mg, and 31.1% with placebo. Overall, the most common AE was peripheral oedema which occurred most frequently with amlodipine 10 mg (12.6%) compared with 9.5% with valsartan/amlodipine 320/10 mg, 0% with valsartan 320 mg, and 1.0% with placebo. Other frequently occurring AEs (> 1%) with valsartan/amlodipine 320/10 mg were nasopharyngitis (2.4%), upper respiratory tract infection (2.4%), dizziness (1.9%), asthenia (1.4%), and fatigue (1.4%), all of which were reported more frequently with the combination than with placebo. All other AEs reported with valsartan/amlodipine 320/10 mg occurred with a frequency of≤ 1% (that is,≤ 2 patients). Orthostatic hypotension was reported in 8.7% of valsartan/amlodipine 320/10 mg treated patients, 9.2% with valsartan 320 mg, 10.2% with amlodipine 10 mg, and 5.3% with placebo.

f. It is considered that the long-term (54-week) efficacy and safety of valsartan/amlodipine 320/5 mg has been satisfactorily established. In the long-term, 54-week, open-label extension study [2307E1], 310 patients were exposed to combination valsartan/amlodipine 320/5 mg for at least 180 days and 115 for at least 362 days. The incidence of adverse events in the 403 patients treated in the extension phase was 41.4%. The most frequently reported AEs were bronchitis (4.5%), back pain (2.5%), nasopharyngitis (2.5%) and sinusitis (2.2%). Most AEs were mild to moderate in intensity, and not suspected to be related to the study drug. There were no deaths, and SAEs (4.2%; n=17) and other significant AEs (3.2%; n=13) did not give rise to concern. The changes in haematology and biochemistry parameters were clinically unremarkable. The incidence of orthostatic hypotension occurring at one or more study visit was 5.5% over 54 weeks. Overall, there were no unexpected safety concerns observed in the long-term study, and the safety profile of the valsartan/amlodipine 320/5 mg combination was consistent with the known profiles for its components. The submission included no long-term safety data on the valsartan/amlodipine 320/10 mg combination, but it is considered that the totality of the safety data on the combinations provided in the previous and current submissions, and the well established safety profiles of both valsartan 320 mg and amlodipine 10 mg, show that the combination can be administered safely over the long-term.

g. The submission did not include studies which allowed for a direct comparison of valsartan 320/5 mg and 320/10 mg combinations. The cross-study comparison showed that the placebo-subtracted LS reduction in mean±SE sitting diastolic blood pressure with valsartan 320/5 mg was 9.19 mmHg±0.920 [study 2201] compared with 9.87±0.79 with valsartan 320/10 mg [2307]. Similar results for the two combinations were also seen for placebo-subtracted reductions in mean sitting systolic blood pressure. The cross-study comparison suggests similar results for reduction in blood pressure for valsartan 320/5 mg and 320/10 mg combinations. However, the placebo-response rate for change in the mean sitting diastolic and systolic blood pressure in *study 2307* were higher than those in *study 2201,* which might at least in part account for the similarity of the placebo-subtracted reductions in sitting blood pressures for the two combinations. However, in the absence a direct comparison between the two combinations in the same study it cannot be concluded that there is no clinically significant difference between the two combinations as regards reduction in blood pressure. Both valsartan/amlodipine 320/5 mg and valsartan/amlodipine 320/10 mg combinations are efficacious and it is considered clinically reasonable to recommend approval of both combinations.

h. In both *study 2201* and *study 2307*, patients treated with valsartan 320/5 mg or valsartan 320/10 mg did not receive the relevant fixed combination tablets of valsartan/amlodipine. Instead, individual valsartan and amlodipine products were given concomitantly (that is, 2 x 160 mg capsules plus 1 x 5 mg amlodipine over-encapsulated

tablet or 2 x 5 mg amlodipine over-encapsulated tablets). However, on the basis of the bioavailability and biopharmaceutical data in the current and previous submissions it is likely that the concomitantly administered valsartan and amlodipine treatments are bioequivalent to the proposed corresponding fixed combination tablets.

Clinical Evaluator's Recommendation

It is recommended that both Exforge (Ejocia) 5/320 and 10/320 film coated tablets be approved as replacement therapy in patients whose blood pressure is adequately controlled on amlodipine besylate and valsartan used as individual 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

The quality evaluator recommended approval with respect to chemistry, quality control and bioavailability. The submission was also considered by the PSC of ACPM who had some concerns with the result for one patient in a bioequivalence study (study 2310) and for the justification for using an overseas amlodipine reference product in the phase III studies and bioequivalence studies. These issues were resolved by the quality evaluator. The results for the study were similar with or without this subject and the dissolution profiles were similar between amlodipine in the combination and Australian Norvasc. The evaluator noted that no bioequivalence study was submitted to establish that the US sourced Norvasc (amlodipine) used in the clinical studies is the same as the Australian Norvasc. However, the evaluator accepted the sponsor's justification and dissolution data and noted that amlodipine can be considered a Biopharmaceuticals Classification Scheme Class I drug with high solubility and permeability; therefore the bioavailability of amlodipine is unlikely to be significantly affected by finished product formulation differences.

Nonclinical

There were no new nonclinical data submitted

Clinical

The clinical data relies on 5 studies that have been previously evaluated by the TGA and seen by ADEC (255th meeting) when the sponsor registered the lower strengths of Exforge/Ejocia, as follows:

Two bioequivalence studies: 320mg/5 versus 320 and 5 mg and separately.

Three clinical studies: 2 placebo controlled 8 week studies using 320/5 mg and 320/10 mg and a 54 week extension study using 320/5 mg.

The clinical evaluator recommended approval of the submission. The issues noted by the evaluator in this submission included:

There were no add-on clinical trials in which patients stabilised on 320mg valsartan or 5 or 10mg amlodipine were switched to the corresponding fixed dose combination (both 8 week studies compared combination with individual components).

No bioequivalence study was submitted between 320/10mg and 10mg amlodipine or 320mg valsartan however an acceptable justification was provided.

No food effect study was submitted, but this was previously assessed for the lower strengths.

No direct comparison of 320/5 mg with 320/10mg.

No long term efficacy or safety data for 320/10mg, but there was for the 320/5mg.

Pharmacology

The first bioequivalence study failed to demonstrate bioequivalence between 320/5mg and its components which led the sponsor to change the formulation from a monolayer to a bilayer design. A second bioequivalence study [2310] was then conducted which demonstrated that 320/5mg was bioequivalent to the free combination of 5mg amlodipine (US source) and 320mg valsartan (Switzerland source). Previously submitted data have demonstrated that the valsartan used is bioequivalent to the Australian valsartan and the use of US sourced amlodipine is discussed above. The bioequivalence results for valsartan were C_{max} ratio 0.91 (90% CI 0.85-0.98) and AUC_{0-t} ratio 0.95 (0.90-1.00). The results for amlodipine were C_{max} ratio 0.99 (90% CI 0.97-1.02) and AUC_{0-t} ratio 0.99 (0.96-1.02). A justification for not conducting a bioequivalence study on the 320/10mg was also provided.

Efficacy

Study 2201: A multinational, multicentre, randomised double blind, placebo controlled, multi-factorial parallel trial of 320/5mg in 127 patients with mild to moderate hypertension for 8 weeks who were force titrated to this dose from 2.5/160mg after one week. The 320/5mg arm which was compared to 5mg amlodipine, 320mg valsartan and placebo was part of this 15 treatment group study that randomised 1911 patients. Study completion was 91% with maximum benefit seen at 2 weeks. The results are:

Primary efficacy endpoint of change in sitting diastolic blood pressure from baseline showed a significant reduction on 320/5mg of -15.74mmHg with a significantly greater difference compared to 5mg amlodipine (-4.48mmHg) and to 320mg valsartan (-2.54mmHg).

Secondary endpoint of change in sitting systolic blood pressure from baseline showed a significant reduction on 320/5mg of -22.37mmHg with a significantly greater difference compared to 5mg amlodipine (-7.67mmHg) and to 320mg valsartan (-7.07mmHg).

Responder rates (diastolic BP <90mmHg or >10mmHg decrease from baseline) were significantly higher on 320/5mg at 91.3% compared to 5mg amlodipine (71.9%) and 320mg valsartan (73.4%).

Control rates (diastolic BP <90mmHg) were significantly higher on 320/5mg at 82.5% compared to 5mg amlodipine (64.8%) and 320mg valsartan (67.2%).

Study 2307: A multinational, multicentre, randomised double blind, placebo controlled, multi-factorial parallel trial of 320/10mg in 210 patients with mild to moderate hypertension for 8 weeks who were force titrated to this dose from 5/160mg after one week. The 320/10mg arm which compared to 10mg amlodipine, 320mg valsartan and placebo was part of this 6 treatment group study that randomised 1250 patients. Study completion was 93% with maximum benefit seen at 4 weeks. The results are:

Primary efficacy endpoint of change in sitting diastolic blood pressure from baseline showed a significant reduction on 320/10mg of -18.15mmHg with a significantly greater difference compared to 10mg amlodipine (-3.01mmHg) and to 320mg valsartan (-5.33mmHg).

Secondary endpoint of change in sitting systolic blood pressure from baseline showed a significant reduction on 320/10mg of -26.95mmHg with a significantly greater difference compared to 10mg amlodipine (-4.25mmHg) and to 320mg valsartan (-8.52mmHg).

Responder rates (diastolic BP <90mmHg or >10mmHg decrease from baseline) were significantly higher on 320/10mg at 87.5% compared to 320mg valsartan (72%) but not compared to 10mg amlodipine (86.9%).

Control rates (diastolic BP <90mmHg) were significantly higher on 320/10mg at 84.1% compared to 320mg valsartan (63.8%) but not compared to 10mg amlodipine (80.1%).

Study 2307E1: This was an open label 54 week study of 320/5mg in 403 patients with mild to moderate hypertension recruited from study 2307. The criteria were as for study 2307 but also required patients to be well controlled for their BP and no drug related serious adverse events from the previous study. Some 214 patients completed 6 months and 147 patients completed 12 months treatment as per the European Union (EU) guideline. The results demonstrated maintenance of efficacy in reduction in blood pressure of -24.2/-17.0mmHg at endpoint.

Safety

Total exposure to the combination of amlodipine and valsartan was 1437 patients across the two short term studies using different strength combinations, with 337 patients receiving either of the two new doses proposed for 8 weeks. Adverse events in studies 2201/2307 were seen in 46.5%/32.4% on 320/5mg or 320/10mg, 49.2%/28.4% on 320mg valsartan alone, 50.8%/38.2% on 5mg or 10mg amlodipine alone and 50%/31.1% on placebo with no dose response. The most frequent events on 320/5mg were headache (5.5%), dizziness (3.9%), diarrhoea (3.1%), nasopharyngitis (3.1%), bronchitis (2.4%), dyspepsia (2.4%), fatigue (2.4%), limb injury (2.4%) and peripheral oedema (2.4%) which were comparable to other treatment arms. The most frequent events on 320/10mg were peripheral oedema (9.5% versus. 12.6% on 10mg amlodipine), nasopharyngitis (2.4%), upper respiratory tract infection (2.4%), dizziness (1.9%), asthenia (1.4%) and fatigue (1.4%) which were comparable to other treatment arms. Adverse drug reaction rates were similar across the treatment arms. In study 2210, oedema of any type was less on 5/30mg (2.4%) compared to all other arms (320mg valsartan was 3.9%, 5mg amlodipine was 3.2% and placebo was 7%) and in study 2307, oedema of any type was less on 320/10mg (9.5%) compared to 10mg amlodipine (13.5%) but greater than 320mg valsartan (0%) and placebo (1.4%). No deaths were reported in any study and serious adverse events were very low (1 patient on 320/5mg, 2 patients on 320/10mg). Discontinuations due to adverse events were also low (2 patients on 320/5mg and 5 patients on 320/10mg). Laboratory changes were mostly unremarkable and similar to other treatment arms except for some changes in CK levels. Orthostatic hypotension was seen in 10.3% on 320/5mg, 8.7% on 320/10mg, 9.2-13.3% for 320mg valsartan, 10.2% for 5mg amlodipine, 10.2% for 10mg amlodipine and 5.3-11% for placebo.

In the extension study, 310 patients were exposed for >6 months and 115 for 12 months. Adverse events were seen in 41.4% with the most common being bronchitis (4.5%), back pain (2.5%), nasopharyngitis (2.5%) and sinusitis (2.2%). Oedema of any type was seen in 2.2%. Serious adverse events were seen in 4.2% with no patterns, no deaths were reported and adverse events leading to discontinuation were 3.2%. Laboratory results were mostly unremarkable except for 6.4% with >50% increase in white blood cell count consistent with bronchitis, nasopharyngitis and sinusitis, 10.9% with BUN >50% increase, 9.4% with >20% increase in potassium, 2.8% with >150% increase in ALT, 1.3% with >50% increase in

creatinine and 1% with >300% increase in CK. Orthostatic hypotension was seen in 1.3% at study endpoint.

Risk-Benefit Analysis

Efficacy: The data demonstrated bioequivalence between 320/5mg versus 5mg amlodipine (US formulation) and 320mg valsartan separately. Sufficient data and justification have been provided to demonstrate the similarity between the US amlodipine and the Australian Norvasc, based on the previous submission for the lower strengths, dissolution data and amlodipine belonging to BCS class I. No bioequivalence study was submitted between 320/10mg and 10mg amlodipine or 320mg valsartan, however the justification for not providing a study was deemed acceptable by both evaluators. The effect of food was investigated in the previous submission. Two short term clinical studies of 8 weeks duration demonstrated significantly greater efficacy of 320/5mg versus. 5mg amlodipine or 320mg valsartan alone for diastolic and systolic BP, responder rate and control rate and significantly greater efficacy of 320/10mg versus. 10mg amlodipine or 320mg valsartan alone for diastolic and systolic BP, responder rate and control rate (except against 10mg amlodipine). The evaluator considered the long term efficacy to be satisfactorily established for 320/5mg and noted that although the cross study comparison suggested similar blood pressure lowering effects for 320/5 and 320/10mg (that is, implying no dose response), it cannot be concluded there is no difference as there is no direct comparison study. No add-on studies were submitted and there are no long term data on the 320/10mg or clinical outcome data.

Safety: The data have demonstrated the short term safety of the combination with no new or unexpected safety issues appearing in either 8 week studies. Adverse events overall were similar on the combination compared to the monotherapies. Noted events included peripheral oedema and orthostatic hypotension which occurred at a similar rate on the monotherapies. The evaluator considered the long term safety to be satisfactorily established with 115 patients exposed for 362 days on 320/5mg with the most common adverse events being bronchitis, back pain, nasopharyngitis and sinusitis. These events were mostly considered unrelated to study medication. There were no deaths and minimal serious adverse events with minimal laboratory findings. There are no long term data on 320/10mg, however the acceptable safety from the long term 320/5mg study, previous studies and well established safety profiles for amlodipine 10mg and valsartan 320mg provide some reassurance.

Indication: Both amlodipine and valsartan are registered in Australia individually for the treatment of hypertension and in combination for the treatment of hypertension as Exforge/Ejocia. Fixed dose combination products are usually second line products in the treatment of hypertension when a patient has failed one of the components and then a second agent is added to the regimen in the form of the fixed combination product. Such indications require clinical trial data to demonstrate the benefit of adding a second agent to the treatment protocol and that data support dose titration. In the current Australian submission, the sponsor is requesting a different indication for its higher strength combination compared to the currently approved lower strengths which have the standard second line indication. For these new strengths, a patient must already be on both component medicines as individual products and then only when stable on those treatments could the doctor then substitute the two products for this single fixed combination product at the same dose level. This is known as a substitution or replacement indication. The EU guideline on this matter notes the data requirements are usually pharmacokinetic and occasionally pharmacodynamic if needed but Novartis has also supplied clinical data to support the higher strength combinations. There is some potential for confusion for prescribers with two different indications within the same product range, therefore the PI will need to be clear on this matter for prescribing.

Dose titration: Given the wording of the indication is a substitute for patients stable on both monotherapies, then if there was a need to adjust up or down, the indication would imply that a patient would be required to return to separate component drugs, with one or both of them at the new dose, be that higher or lower. Only then once blood pressure control is re-established at the new dose level could the fixed dose combination product be substituted. There are no clinical data that directly tested dose titration between the two new strengths or from the lower strengths to these new higher strengths, although there is with each monotherapy. Therefore the PI should be clear that any dose adjustments should be using the separate component products.

Data deficiencies: There are no clinical outcome studies, no long term clinical studies on the combination of 320/10mg, no studies in renal or hepatic impairment, no studies on withdrawal or rebound effects, no studies directly comparing 320/5 with 320/10mg and no add-on studies.

Summary: The efficacy and safety of amlodipine / valsartan have been demonstrated in three clinical studies along with acceptable bioequivalence. The main issues are the indication wording, addressing dose adjustments and potential for confusion when switching from lower combination strengths to these higher strengths in light of the change in indication.

Recommendation

The Delegate proposed to **approve** this submission by Novartis Pharmaceuticals Australia Pty Ltd to register the two new higher strengths of Exforge/Ejocia 320/5 and Exforge/Ejocia 320/10 (amlodipine / valsartan), based on the quality, safety and efficacy of the product being satisfactorily established for the indication below, and for the reasons stated above in the Risk / Benefit Discussion:

Exforge/Ejocia 320/5 and Exforge/Ejocia 320/10 are indicated as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled with separate doses of amlodipine and valsartan given concurrently at the same dose level. Treatment should not be initiated with this fixed dose combination.

The sponsor should address the following issues in their Pre-ACPM response:

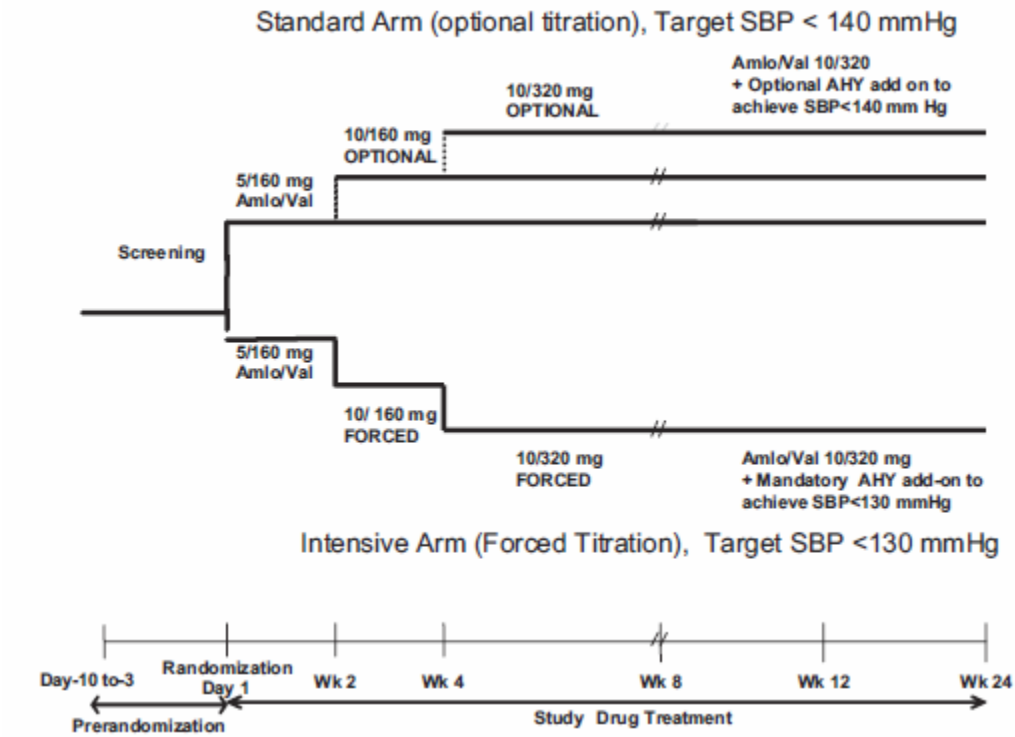
1. An update to the registration status (with dates) for this submission of amlodipine / valsartan in the USA, Europe/UK, Canada and New Zealand including any withdrawals, rejections or deferrals.

   Sponsor's response: Registration status was updated (see *Regulatory status* above).
2. Are any add-on studies being conducted using 320/5 or 320/10 or long term studies using 320/10?

Sponsor's response:
No add-on clinical trials have been conducted in which patients stabilized on 320 mg Valsartan or 5 or 10 mg amlodipine were switched to the corresponding fixed dose combination. However, a study (VAA AUS01) was completed subsequent to the submission that involved titration from 5/160 mg to 10/160 mg to 320/10 mg with patients suffering from hypertension and diastolic dysfunction, and recently published in 'Hypertension-The Journal of the American Heart Association'[10]. VAA AUS01 is an open-label study with a blinded primary endpoint of early diastolic myocardial velocity to evaluate differences in intensive versus standard blood pressure lowering. The study design is presented below:

[10] Solomon SD *et al.*(2010). Effect of Intensive Versus Standard Blood Pressure Lowering on Diastolic Function in Patients With Uncontrolled Hypertension and Diastolic Dysfunction. *Hypertension* 55;241-248.

Figure 4: Titration scheme and study time lines. Patients were dispensed open-label medication depending on treatment assignment, and to reach target, study drug was titrated in the following treatment steps: (1) valsartan 160 mg plus amlodipine 5 mg; (2) valsartan 160 mg plus amlodipine 10 mg; and (3) valsartan 320 mg plus amlodipine 10 mg. Patients in the intensive target arm (SBP 130 mm Hg) had their study medication force titrated to the maximum dose of valsartan 320 mg plus amlodipine 10 mg over the course of the first 4 weeks so as to achieve as low an systolic blood pressure (SBP) as tolerated. AHY indicates antihypertensive therapy.



Even though patients were titrated from 5/160 mg to 10/160 mg to 320/10 mg, the study design does not allow any definitive conclusions regarding blood pressure reductions between doses. The following statement is therefore proposed for inclusion page 8 of the PI:

> *"There have been no studies conducted to evaluate as a primary endpoint the additional blood pressure lowering effects of direct titration of patients from Exforge 10/160 mg or below to the higher strengths of* 320/5 *mg or* 320/10 *mg."*

3. Are any clinical outcome studies on cardiovascular morbidity or mortality being conducted using Exforge?

Sponsor's response:
No clinical outcomes studies on cardiovascular morbidity and mortality have been conducted with amlodipine/valsartan fixed-dose combinations.

ACPM's advice is requested on the following issues: Could having different indications for lower strengths of Exforge/Ejocia (that is, 2nd line hypertension) and higher strengths of Exforge/Ejocia (that is, substitution therapy in hypertension) within the same product range for hypertension treatment be potentially confusing?

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded 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.

The ACPM recommended approval of the submission from Novartis Pharmaceuticals Pty Ltd to register new fixed combination strengths for amlodipine (as besylate) and valsartan (Exforge/Ejocia) tablets 320/5 mg and 320/10 mg film coated tablets, for the indication:

> Exforge / Ejocia is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed dose combination.

In making this recommendation the ACPM considered it potentially confusing to have a mixture of indications across the dose strengths and were satisfied that the clinical trials submitted were adequate to support the indication above for the new strengths. ACPM advised the importance of ensuring consistent wording across the various dosage strengths for this product and across all fixed dose combinations for hypertension treatment in regard to treatment not being initiated with fixed dose combinations.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Exforge/ Ejocia 320/5 and Exforge/Ejocia 320/10, one tablet per day, indicated for:

> The treatment of hypertension. Treatment should not be initiated with this fixed dose combination.

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.

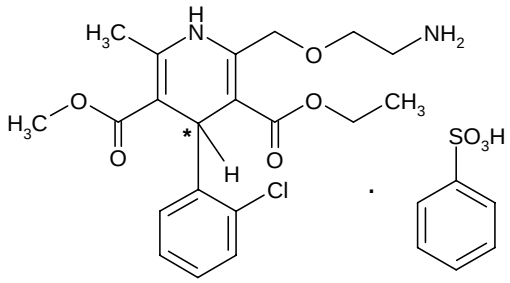
EXFORGE HCT 5/160/12.5®
EXFORGE HCT 5/160/25®
EXFORGE HCT 10/160/25®
EXFORGE HCT 10/160/12.5®
EXFORGE HCT 10/320/25®

(amlodipine besylate/valsartan/hydrochlorothiazide)

NAME OF THE MEDICINE

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

Structural formula:



and enantiomer

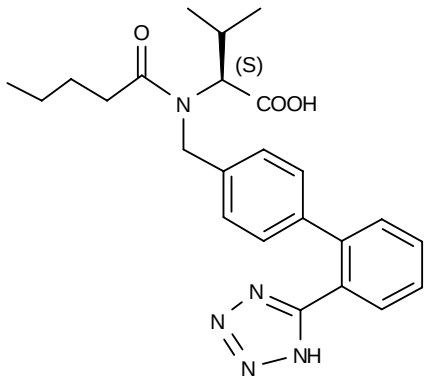
Amlodipine (as the besylate salt)

(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

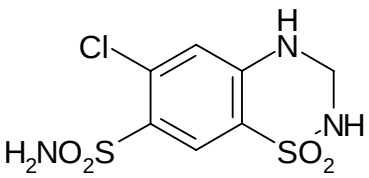


Valsartan

(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

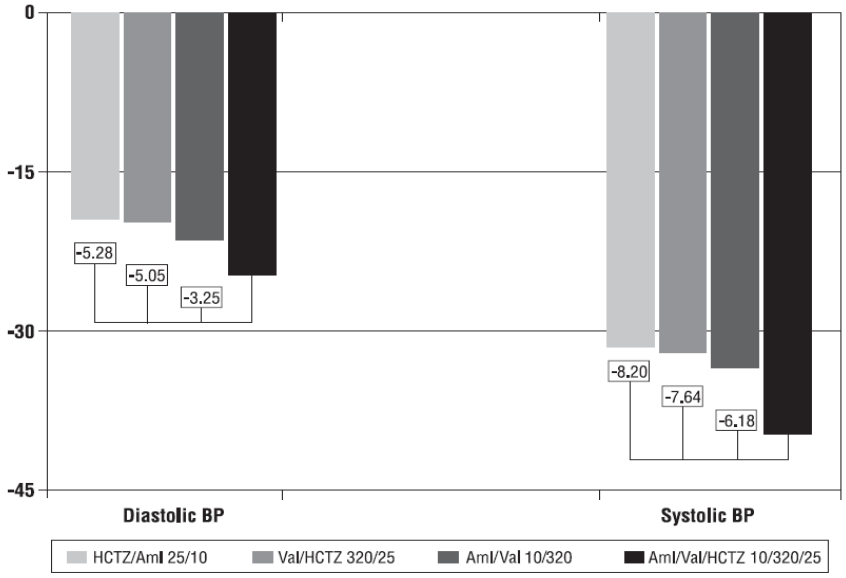


Figure 2: Mean Sitting Diastolic Blood Pressure by Treatment and Week

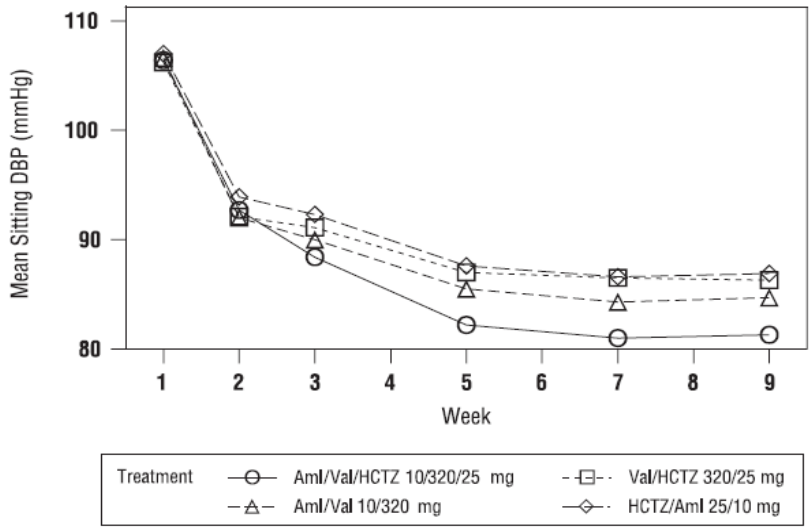
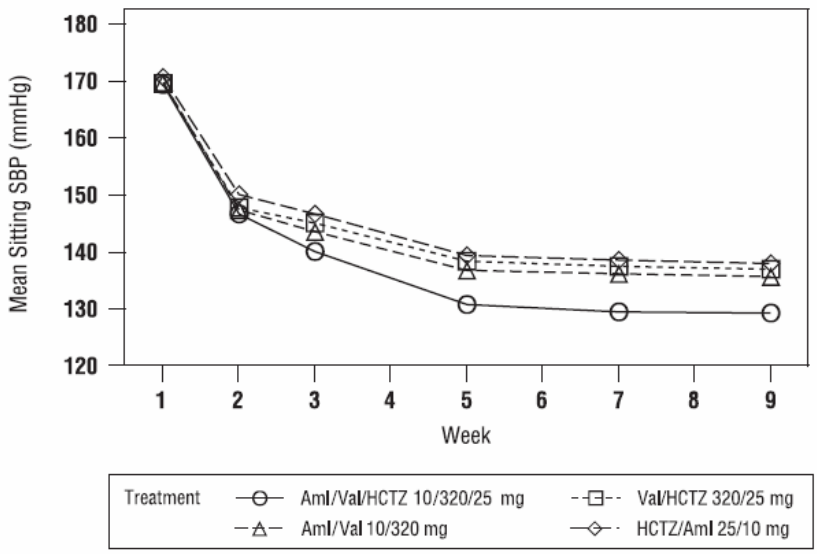


Figure 3: Mean Sitting Systolic Blood Pressure by Treatment and Week



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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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.

Therapeutic Goods Administration

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