Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Telmisartan/Amlodipine

Proprietary Product Name: Twynsta

Sponsor: Boehringer Ingelheim Pty Ltd

March 2011

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	New Fixed Dose Combination
Decision:	Approved
Date of Decision:	14 February 2011
Active ingredient(s):	Telmisartan Amlodipine (as besylate)
Product Name(s):	Twynsta
Sponsor's Name and Address:	Boehringer Ingelheim Pty Ltd 78 Waterloo Road North Ryde NSW 2113
Dose form(s):	Tablet
Strength(s):	40 or 80 mg of telmisartan and 5 or 10 mg of amlodipine
Container(s):	Blister pack
Pack size(s):	Packs of 7, 14, 28, 30, 56 and 98
Approved Therapeutic use:	Treatment of hypertension. Treatment should not be initiated with this fixed-dose combination (see Dosage and Administration).
Route(s) of administration:	Oral
Dosage:	One daily
ARTG Number (s)	166263, 166264, 166265 and 166266

Product Background

This AusPAR describes the evaluation of a submission is to register the new fixed-dose combination product, Twynsta, which has been developed as bilayer tablets, each layer containing either 40 mg or 80 mg telmisartan and 5 mg or 10 mg amlodipine (as besylate), respectively.

Four different dose combinations are proposed for registration:

Proposed Product Tradename	*Strength(s)*	*Combination of Active Ingredients*	
		Telmisartan	*Amlodipine (as besylate)*
TWYNSTA®	**40/5 mg**	40 mg	5 mg
	40/10 mg	40 mg	10 mg
	80/5 mg	80 mg	5 mg
	80/10 mg	80 mg	10 mg

The proposed indications are as follows:

Treatment of hypertension.

Replacement therapy

Patients receiving telmisartan and amlodipine from separate tablets can instead receive Twynsta containing the same component doses.

Add on therapy

Twynsta is indicated in patients whose blood pressure is not adequately controlled on telmisartan or amlodipine monotherapy.

Initial therapy

Twynsta 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 Twynsta as initial therapy for hypertension should be based on an assessment of potential benefits and risks.

The fixed dose combination product (FDC) product in this submission consists of two drugs that have already been approved and are established for the treatment of essential hypertension: telmisartan (an angiotensin receptor blocker [ARB]) and amlodipine (a calcium channel blocker [CCB]).

Telmisartan is an orally active, non-peptide type I ARB. It lowers blood pressure (BP) with once-daily dosing by blocking the type I angiotensin II receptor (AT1 receptor), thus, selectively inhibiting the pressor effects of the renin angiotensin aldosterone system (RAAS). Amlodipine is a dihydropyridine CCB that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle cells. It is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in BP.

Based on the fact that many patients with hypertension will require two or more antihypertensive medications to achieve their BP goals and that combination of an ARB and amlodipine in the treatment of hypertension can be considered established clinical practice, a clinical development program was undertaken to evaluate a FDC combining telmisartan and amlodipine.

Micardis tablets containing 40 and 80 mg of telmisartan were approved for registration by Boehringer Ingelheim Pty Ltd in August 1999 with the indications, '*treatment of hypertension*' and '*prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes with evidence of end organ damage*'. Identical products have also been registered with the trade name Pritor. There are no generics.

Micardis Plus (and Pritor Plus) '40/12.5', '80/12.5' and '80/25' fixed dose combination tablets of telmisartan with hydrochlorothiazide were registered to Boehringer Ingelheim Pty Ltd in September 2008 (and March 2010) with the simpler indication of '*treatment of hypertension*' with the condition that '*treatment should not to be initiated with this fixed dose combination*'. There are no generics.

Tablets containing the 2.5, 5 and 10 mg of amlodipine (as the besylate) have been registered for many years (1993) for the use in the treatment of hypertension. Pfizer (Norvasc) would appear to be the innovator but there are many generics. Fixed dose combination tablets with valsartan (Novartis), olmesartan medoxomil (Schering Plough) and atorvastatin (as calcium; Pfizer) have been registered.

Regulatory Status

A similar application to the current Australian application was approved in the USA on 16 October 2009), in the European Union (EU) on 7 October 2010 and in Switzerland on November 2010. An evaluation is ongoing in Canada. The indication in the US is as follows:

Twynsta is an angiotensin II receptor blocker (ARB) and a dihydropyridine calcium channel blocker (DHP-CCB) combination product indicated for the treatment of hypertension alone or with other antihypertensive agents

Twynsta tablets are indicated as initial therapy in patients likely to need multiple antihypertensive agents to achieve their blood pressure goals

The indication in the EU is:

Treatment of essential hypertension in adults:

Add on therapy

Twynsta is indicated in adults whose blood pressure is not adequately controlled on amlodipine.

Replacement therapy

Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Twynsta containing the same component doses.

Product Information

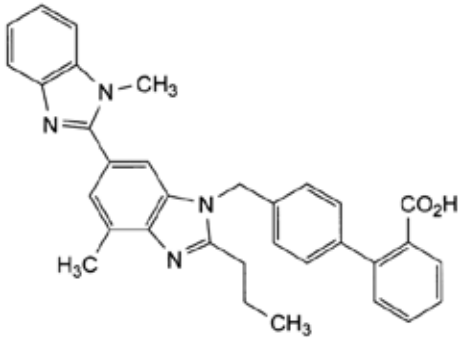
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substances (active ingredients)

There is a European Pharmacopoeia (EP)/British Pharmacopoeia (BP) monograph for amlodipine besilate[1] and a United States Pharmacopoeia (USP) monograph for amlodipine besylate. There is also an EP/BP monograph for telmisartan, but there is no USP monograph for telmisartan and no compendial monographs for the finished product.

Structures and other details of the drug substances are shown below:



telmisartan

Chemical Name (from BP):
4'-[[4-methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

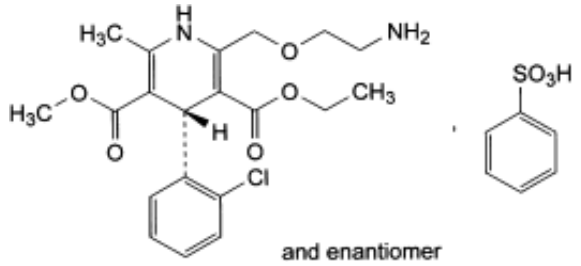
CAS Number: [144701-48-4]

Molecular Formula: $C_{33}H_{30}N_4O_2$ *Molecular Weight*: 514.63

Description: A white or yellowish crystalline powder

Solubility in Water: Practically insoluble <0.1 mg/mL (<0.01 %w/v)

[1] Note the Australian Approved Name (AAN) at the time of writing is amlodipine besylate and not amlodipine besilate but it will be referred to as simply amlodipine for the remainder of this AusPAR..



amlodipine besylate

Chemical Name:
3-ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate

CAS Number: [111470-99-6] ([88150-42-9] for free base)

Molecular Formula: $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$

Molecular Weight: 567.1 (408.9 for free base)

Description: A white to almost white powder

Solubility in water: Slightly soluble (1.0-10 mg/mL, 0.1-1.0%)

The details relating to telmisartan drug substance are basically the same as for the registered products, but some tightening of limits has taken place to ensure compliance with the EP6.6/BP2010 monograph for telmisartan[2].

The amlodipine besylate used in the products is covered by an EDQM Certificate of Suitability certifying that the material meets the EP6.6/BP2010 monograph for amlodipine. In addition, the finished product manufacturer has adopted additional tests and limits for particle size distribution and residual solvents. The sponsor provided data to demonstrate that levels of alkyl besylates (which are genotoxic and can be formed from besylate ions and methanol, ethanol or isopropanol used in the manufacture of amlodipine besylate) are much lower (<10 parts per million [ppm]) than levels that would be of concern (total 150 ppm).

Drug Product

The tablets are bi-layered with the amlodipine layer compressed on to the compressed telmisartan layer.

- The telmisartan granulate is manufactured by the dissolution of telmisartan in sodium hydroxide solution with povidone and meglumine. Due to this dissolution, the particle size distribution of telmisartan is not critical. The mixture is spray-dried and screened. This granulate is mixed with further excipients and compressed to give what is termed the 'telmisartan layer'.
- The 'amlodipine layer' is made by dry granulation.
- The bi-layered tablets are then packaged.

The tablets contain no unusual excipients and the quality of the excipients is adequately controlled. No material of animal origin is used.

[2] The sponsor is going to make similar changes in relation to the registered telmisartan products.

The same telmisartan layer is used in all tablets, but the mass taken for the tablets containing 80 mg of telmisartan is twice the mass taken for the tablets containing 40 mg of telmisartan (that is, the telmisartan layers are in direct scale). This layer is white.

The mass of the amlodipine layer used is kept constant with the different amount of amlodipine in the 5 and 10 mg tablets being compensated for with different amounts of microcrystalline cellulose. This layer is blue.

All the tablets are the same shape (oval) and thus the tablets containing 40 and 80 mg telmisartan are distinguished by size. However the pairs '40/5' and '40/10', and '80/5' and '80/10', are basically the same size, shape and colour. The tablets are distinguished by markings ("A1", "A2", "A3", "A4"). They are further distinguished by the packaging with a different colour for each strength which clearly marks each strength and includes the statement 'Store in original packaging'. The Delegate considered it preferable that each strength tablet be a different colour or have markings that directly represent the strengths but did not state this was a requirement. It was accepted that the tablets and packaging represent sufficient distinction. None of the tablets are scored.

The tablets are well controlled with satisfactory expiry limits and release limits that allow for some change on storage, though no such change was noted. All of the telmisartan degradants and amlodipine degradants have expiry limits at or below the International Council on Harmonisation (ICH) qualification thresholds of 0.2% and 0.5%, respectively.[3]

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

Bioavailability

Clinical Background

The Phase III clinical efficacy studies in relation to add-on therapy and initial therapy were performed with the proposed fixed dose combination (FDC) tablets and no comparative bioequivalence data were required in this respect. However, as the tablets can also be a replacement therapy, the bioequivalence of the proposed FDC tablets to the Australian monotherapy tablets must be demonstrated.

Studies submitted

The sponsor submitted three bioavailability studies, two pharmacokinetic interaction studies, a justification for not generating bioavailability data using two of the tablet strengths ('40/10' and '80/5') and a justification for using the US comparator in two of the bioavailability studies.

The test methods used in the studies to determine levels of telmisartan and amlodipine in subjects' plasma samples were evaluated and found to give accurate and precise results. Further subject samples were collected at appropriate times to allow good estimation of the pharmacokinetic parameters including the maximal plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC).

[3] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Study 1235.3 (Document U08-1586-01, Bioequivalence)

This study compared the proposed FDC 40/5 tablet to co-administration of the separate monotherapy tablets (registered Micardis 40 mg + US-bought Norvasc 5 mg) at a dose of 80/10 mg. It was an open-label, single-dose two-way crossover study in 84 healthy subjects (42 male, 42 female, all completed), with both treatments administered in the morning following an overnight fast.

The results (Table 1) indicated that in relation to both telmisartan and amlodipine the FDC 40/5 tablet was bioequivalent to the corresponding dose of co-administered Micardis and US-Norvasc.

Table 1: Pharmacokinetic parameters in Study 1235.3

Parameter	Geometric Mean Ratio (FDC/Separate) and [90% Confidence Intervals]	
	Telmisartan	Amlodipine
$AUC_{0-\infty}$	0.980 [0.923-1.041]	1.004 [0.981-1.027]
Cmax	1.061 [0.958-1.175]	1.000 [0.973-1.027]

Study 1235.4 (Document U08-1563-01, Bioequivalence)

This study compared the proposed FDC 80/10 tablet to co-administration of the separate monotherapy tablets (registered Micardis 80 mg + US-bought Norvasc 10 mg) at a dose of 80/10 mg. It was an open-label, single-dose two-way crossover study in 84 healthy subjects (42 male, 42 female, 81 completed), with both treatments administered in the morning following an overnight fast.

The results (Table 2) indicated that in relation to both telmisartan and amlodipine the FDC 80/10 tablet was bioequivalent to the corresponding dose of co-administered Micardis and US-Norvasc.

Table 2: Pharmacokinetic parameters in Study 1235.4

Parameter	Geometric Mean Ratio (FDC/Separate) and [90% Confidence Intervals]	
	Telmisartan	Amlodipine
$AUC_{0-\infty}$	1.033 [0.986-1.083]	1.056 [1.033-1.079]
Cmax	1.082 [0.977-1.197]	1.029 [1.005-1.054]

Study 1235.12 (Document U08-1587-01, Food Effect)

This study compared the proposed FDC 80/10 tablet after an overnight fast and after a standard high fat breakfast. It was an open-label, single-dose two-way crossover study in 40 healthy subjects (20 male, 20 female, 39 completed).

The results (Table 3) indicated that food does not affect the bioavailability of amlodipine from the proposed 80/10 tablets. However, the food reduces the bioavailability of telmisartan (AUC by 24% and C_{max} by 60%). This result was brought to the attention of the Delegate.

Table 3: Pharmacokinetic parameters in Study 1235.12

Parameter	Geometric Mean Ratio (Fed/Fasted) and [90% Confidence Intervals]	
	Telmisartan	Amlodipine
$AUC_{0-\infty}$	**0.757**	1.077

	[**0.712-0.805**]	[1.037-1.118]
Cmax	**0.399** [**0.331-0.481**]	1.043 [1.003-1.085]

Study 1235.2 (Document U08-1163-01, Interaction)

This was a two-way crossover pharmacokinetic (PK) interaction study where the registered 80 mg telmisartan tablet was administered separately or in combination with 2 x 5 mg amlodipine tablets (US-Norvasc). This study was only briefly evaluated.

After a single-dose and at steady state (Day 9) the results indicated that amlodipine does not affect the bioavailability of telmisartan.

Study 502.126 (Document U96-2540, Interaction)

This was a two-way crossover PK interaction study where 2 x 5 mg amlodipine tablets (US-Norvasc) were administered separately or in combination with 3 x 40 mg telmisartan tablets (not as registered). This study was only briefly evaluated.

After a single-dose and at steady state (Day 9) the results indicate that amlodipine does not affect the bioavailability of telmisartan.

Justifications for Not Performing Bioavailability Studies

Intermediate Strengths

No data were included comparing the 40/10 and 80/5 strengths to the appropriate combination of monotherapy tablets or to the proposed 40/5 or 80/10 tablets. The justification for this was acceptable on both chemical and clinical grounds. The dissolution profile results of all four strengths at pH 1, 4.5 and 7.5 (telmisartan) or pH 2, 4.5, 6.8 (amlodipine) were similar.

Overseas Reference Product

No data were included comparing an Australian registered amlodipine tablet to the US-Norvasc amlodipine tablet used in the bioequivalence studies. The justification of this was acceptable on both chemical and clinical grounds. It was noted that at the proposed maximum daily dose (10 mg), amlodipine can be considered a BCS Class 1 and the dissolution profile results of 5 and 10 mg US-Norvasc and 5 and 10 mg Australian Norvasc tablets at pH 2, 4.5 and 6.8 were similar.[4]

Consideration by the Pharmaceutical Subcommittee (PSC) of ACPM

Details of this submission were presented at the 134th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescriptions Medicines (ACPM) in September 2010. The PSC:

- Considered the justifications for not providing bioavailability data on all strengths of the fixed-dose combination tablets and for using an overseas formulation of amlodipine tablets in the bioavailability studies acceptable.
- Supported that the Delegate should be informed of the magnitude of the effect of food on the bioavailability of telmisartan (a reduction in AUC by 24% and C_{max} by 60%).

[4] 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.

Quality Summary and Conclusions

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

In relation to bioavailability:

- Data were provided to demonstrate that the proposed fixed-dose combination tablets can be a replacement therapy in patients already receiving telmisartan and amlodipine from separate tablets.
- Food reduces the bioavailability of telmisartan (but not amlodipine).

III. Nonclinical Findings

Introduction

The sponsor has presented an adequate submission, although small group sizes in pharmacokinetic studies hindered their interpretation. The pivotal repeat-dose toxicity study was performed according to Good Laboratory Practice (GLP) conditions.

Pharmacology

No pharmacodynamic or safety pharmacology studies on individual drug components were performed. This is acceptable, as the mechanism of action of both drugs in the combination is well established and each has a history of extensive research, regulatory review, and post-market experience.

Pharmacodynamic interactions

The sponsor demonstrated, using spontaneously hypertensive rats (SHR), that daily dosing with the telmisartan/amlodipine combination (1/5 mg/kg/day orally [PO]) produced a more rapid onset of BP lowering and a significantly greater reduction in BP as compared with either monotherapy. This efficacy was associated with exposures (mg/m^2-based) 0.2 (telmisartan) and 9.1 (amlodipine) times that of the lowest clinical dose of each drug. The results suggested that the BP lowering effects of telmisartan and amlodipine are additive when used in combination in rats. The BP lowering effects of the fixed combination at clinically relevant amlodipine concentrations are unknown.

No studies were submitted investigating potential pharmacodynamic interactions between the drug combination and other drugs. This was considered acceptable, given the available clinical history with these products.

Pharmacokinetics

Single-dose plasma pharmacokinetics of telmisartan (1 mg/kg PO) and amlodipine (5 mg/kg PO), given alone or in combination, were compared in male normotensive (Sprague Dawley [SD]) and SHR rats. Telmisartan exposure in both rat strains appeared to be unaffected by amlodipine co-medication. Amlodipine exposure was not significantly affected by combination with telmisartan in SD rats; although there was a trend towards increased amlodipine exposure. SHR rats showed significantly higher amlodipine exposure when co-medicated with telmisartan (as compared with treatment with amlodipine alone). Interpretation of these findings was difficult, due to small sample sizes (n=3) and high variance of results. The ratio of telmisartan:amlodipine tested in this study (1:5) was also quite different to any proposed clinical ratio.

The pivotal pharmacokinetic data were obtained as part of an examination of the toxicology of the telmisartan/amlodipine combination. Groups of rats were given a once daily oral dose of telmisartan/amlodipine at 3.2/0.8, 10/2.5, or 40/10 mg/kg, telmisartan at 40 mg/kg, or amlodipine at 10 mg/kg for 13 weeks. As for the single dose study, interpretation of results

was hindered by small group sizes (n=2) and high variability. The major conclusions from the study were:

(1) C_{max} and the area under the plasma concentration time curve from time zero to 24 hours ($AUC_{0\text{-}24\ h}$) values for telmisartan increased approximately in proportion with dose, however, both values for amlodipine increased more than proportionally with dose.

(2) In both sexes and all dose groups, amlodipine and telmisartan exposure on Day 86 were higher than on Day 1.

(3) C_{max} and $AUC_{0\text{-}24\ h}$ values for amlodipine were generally higher in females than males, but there was no consistent effect of gender on plasma concentrations of telmisartan.

(4) Amlodipine toxicokinetics were not significantly influenced by co-administration with telmisartan, although a trend towards reduced amlodipine exposure with combination dosing was observed. Definitive conclusions could not be drawn for telmisartan toxicokinetics, due to anomalous and variable results.

Distribution

Circulating telmisartan and amlodipine are known from previous studies to be largely bound to plasma protein. The sponsor used equilibrium dialysis experiments to demonstrate that the level of binding to human plasma by radioactively tagged telmisartan or amlodipine was not altered by the presence of an excess of the other drug. Hence, telmisartan and amlodipine show no interaction with regard to plasma protein binding under *in vitro* conditions.

In vitro studies with purified proteins indicated that telmisartan bound strongly to GST type l-l and less strongly to albumin (both proteins are present at high concentrations in liver cytosol). Telmisartan slightly inhibited glutathione S-transferase (GST) activity *in vitro* (39% inhibition was observed at 250 µM). Tissue distribution studies in male rats were performed following PO dosing with radioactively tagged telmisartan. Results were generally similar to previous studies with telmisartan with radioactivity predominantly found in liver at all time points investigated. By 48 hours after administration, virtually all the radioactivity had been eliminated from rat tissues. Consistent with *in vitro* experiments above, sub-cellular fractionation experiments showed that nearly 60% of the radioactivity in the liver was present in the cytosolic fraction.

PK drug interactions

The submitted nonclinical data were not adequate to identify potential pharmacokinetic interactions between telmisartan and amlodipine, although the toxicity data did not indicate a cause for concern (see *Repeat dose toxicity* below). Nonclinical PK interaction studies between the dual combination (or components) and other drugs were not performed by the sponsor. Published results indicate that amlodipine, which is metabolised by and also inhibits cytochrome P-450 (CYP) 3A4, can interact with other drugs that are metabolised by CYP3A4. Previous studies showed limited inhibition of CYP2C9 and CYP2C19 activity by telmisartan at high concentrations *in vitro*, although these interactions were not considered clinically relevant.

Toxicology

Relative exposure

Exposure ratios were derived by dividing rat $AUC_{0\text{-}24\ h}$ values by $AUC_{0\text{-}24\ h}$ values at steady state from normal humans (n = 18/sex; age = 18-50 years) given a once daily dose of 80 mg of telmisartan and 10 mg of amlodipine for 9 days (Study 1235.2; see Sections II and IV). The recommended maximum daily dose of Twynsta for adults is one 80/10 mg tablet per day.

The human study gave mean steady state AUC values for telmisartan of 682 and 1460 ng•h/mL and for amlodipine of 269 and 333 ng•h/mL in males and females, respectively. The female steady state AUC values for telmisartan and amlodipine (1460 and 333 ng•h/mL, respectively), being on average significantly higher than those for males, were used as the denominator in calculating exposure ratios (Table 4).

It is notable from Table 4 that exposure ratio values for amlodipine at the No Observable Adverse Effect Level (NOAEL) were only 0.1-0.2. Calculated exposure margins for amlodipine and telmisartan exceeded 10 at the high dose (HD). However, the HD values were based on discordant results that were around 4-times higher than expected based on comparison with single-drug results. The high level of variability in pharmacokinetic parameters due to small group sizes must also be taken into account. Hence, the relative plasma exposure levels at the NOAEL in this study were either less or comparable to those anticipated in humans at the maximum combination dose for the components. Similarly low exposure margins have been noted for these and similar drugs in previous evaluations.

Table 4: Relative exposure to telmisartan and amlodipine during rat 13-week, repeat-dose toxicology study. (The NOAEL is bolded and underlined).

Study no.	Sample time	Drug dose (mg/kg/ d)[c]	Drug	Sex	$AUC_{0\text{-}24\ h}$ (ng.h/mL)	Exposure ratio
DDB0001	Day 1	**3.2/0.8**	Telmi.	M	1,490	1.0
				F	1,520	1.0
			Amlod.	M	34.1	0.1
				F	43.0	0.1
		10/2.5	Telmi.	M	3,020	2.1
				F	4,490	3.1
			Amlod.	M	114	0.3
				F	183	0.5
		40/10	Telmi.	M	9,740	6.7
				F	7,940	5.4
			Amlod.	M	843	2.5
				F	1,490	4.5
		40	Telmi.	M	15,300	10
				F	10,300	7.1
		10	Amlod.	M	1,000	3.0
				F	1,620	4.9
	Day 86	**3.2/0.8**	Telmi.	M	2,390	1.6
				F	2,040	1.4
			Amlod.	M	57.0	0.2
				F	73.9	0.2
		10/2.5	Telmi.	M	4,130	2.8
				F	6,900	4.7
			Amlod.	M	308	0.9
				F	348	1.0
		40/10	Telmi.	M	109,000	75
				F	51,500	35
			Amlod.	M	3,110	9.3
				F	2,980	8.9

		40	Telmi.	M	16,500	11
				F	17,700	12
		10	Amlod.	M	2,970	8.9
				F	4,360	13

Telmi. = telmisartan, Amlod. = amlodipine

Repeat-dose toxicity

The sponsor submitted a 13-week toxicology study in SD rats, involving once-daily PO (gavage) dosing at 3.2/0.8, 10/2.5, or 40/10 mg/kg/day of telmisartan/amlodipine, 40 mg/kg/day of telmisartan or 10 mg/kg/day of amlodipine. This was considered acceptable for a fixed combination corresponding closely to one that is already in widespread use. The repeat-dose toxicology study was performed by an established pharmacology laboratory according to GLP procedures and used both sexes and standard testing times and group numbers. The use of a 4:1 ratio of telmisartan to amlodipine was considered acceptable, as other ratios intended for clinical use (8:1 and 16:1) would likely be dominated by the effects of telmisartan.

The telmisartan/amlodipine combination was well tolerated and no major novel toxicities were observed. Changes that were seen included decreased bodyweight gain, decreases in red blood cell counts and haemoglobin concentration, reduced activated partial thromboplastin time (APTT) levels, elevated plasma urea, creatinine, and phosphorus concentrations, changes in electrolyte levels and decreases in total plasma protein levels. Several organs, including brain and kidney, showed bodyweight relative weight changes after repeat dosing with the combination or the individual drugs. Most findings were largely reversed after the recovery period. The above-described changes have been observed previously as exaggerated pharmacological effects of antihypertensive treatment. For example, the prolonged hypotensive effect of angiotensin II receptor antagonists leads to decreased renal perfusion and subsequent ischaemia which results in increased plasma urea and creatinine concentrations. This is a class effect of drugs that interfere with the Renin Angiotensin Aldosterone System (RAAS) such as angiotensin receptor blockers and angiotensin converting enzyme (ACE) inhibitors. Similarly, angiotensin II receptor blockade has been shown to result in the direct inhibition of erythropoiesis (Naito *et al*. 2003).[5] The changes seen appeared to be largely induced by telmisartan (that is, similar effects typically seen after repeat dosing with 40/10 mg/kg/day of telmisartan/amlodipine or 40 mg/kg/day of telmisartan) and the telmisartan/amlodipine combination did not generally induce additive effects. One exception was the increase in plasma urea concentration where the two drug combination appeared to have an additive effect.

The only histopathology finding was an apparent marked increase in the incidence of cortical tubular basophilia in the kidneys of males that received 40/10 mg/kg/day of telmisartan/amlodipine. Cortical tubular basophilia is thought to be an early stage of chronic progressive nephrosis. However, because spontaneous cortical tubular basophilia is a frequent finding in some strains of laboratory rat (Peter *et al*. 1986), a causal relationship between the high levels of basophilia and the drug treatment is unlikely.[6]

[5] Naito M, Kawashima A, Akiba T, Takanashi M, Nihei H. Effects of an angiotensin II receptor antagonist and angiotensin-converting enzyme inhibitors on burst forming units-erythroid in chronic hemodialysis patients. Am J Nephrol 2003; 23: 287-293.

[6] Peter CP, Burek JD, van Zwieten MJ. Spontaneous nephropathies in rats. Toxicologic Pathology 1986; 14: 91-100.

An important issue to be addressed in the sponsor's study was whether the combination of telmisartan with amlodipine would increase the severity of gastrointestinal tract lesions (for example, gastric erosions and ulcers) that had been observed in a previous study. It was also expected that higher doses of telmisartan would induce significant hypertrophy and hyperplasia of the juxtaglomerular apparatus. Despite attaining exposure margins (AUC) comparable with those associated with gastric lesions in other studies these toxicities were not seen in the current study, perhaps suggesting an effect of rat strain on the occurrence of these endpoints

The nonclinical data presented showed no novel toxicities and suggest that the telmisartan/amlodipine combination presents no novel safety issues of clinical concern.

Genotoxicity, carcinogenicity, and reproductive and developmental toxicity

No studies were submitted for the telmisartan/amlodipine combination under these headings which is acceptable and consistent with the TGA-adopted EU guideline for fixed dose combinations using previously approved components[7]. As noted in the proposed Product Information (PI), Twynsta should not be used in pregnancy. This is consistent with the known effects of angiotensin receptor blockers in the second and third trimesters of pregnancy.

Paediatric use

Twynsta is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

Nonclinical Summary and Conclusions

- The nonclinical data submitted by the Sponsor using the proposed combination consisted of a GLP-compliant 13-week bridging toxicology study (including toxicokinetics), a pharmacodynamic study and a single dose pharmacokinetics study in rats. Several other studies investigating the pharmacokinetics and toxicity of telmisartan alone were also submitted. This was an appropriate data package for a fixed combination of previously approved components.
- The BP lowering effects of telmisartan and amlodipine in combination were additive in spontaneously hypertensive rats, at exposures 0.2 (telmisartan) and 9.1 (amlodipine) times that anticipated at the lowest clinical dose of each.
- Telmisartan was taken up by rat liver and was primarily found in the cytosolic fraction. *In vitro* studies indicated that telmisartan bound strongly to GST type l-l and less strongly to albumin (both proteins are present at high concentrations in liver cytosol).
- There was no evidence for an interaction between telmisartan and amlodipine with respect to plasma protein binding.
- Drug interaction studies were not performed by the sponsor. Published results indicate that amlodipine (which is metabolised by and also inhibits CYP3A4) can interact moderately with other drugs that are metabolised by CYP3A4.
- Toxicokinetic data from the rat 13-week combination toxicity study revealed parameters generally consistent with that seen with each drug administered alone, although interpretation of results was hindered by their high variability. Thus, the submitted

[7] EMEA, Committee for Medicinal Products for Human Use (CHMP), 13 October 2005. Note for Guidance of Fixed Combination Medicinal Products, CPMP/EWP/240/95. http://www.emea.europa.eu/pdfs/human/ewp/024095en.pdf

nonclinical data were not adequate to identify potential pharmacokinetic interactions between telmisartan and amlodipine.

- The telmisartan/amlodipine combination was well-tolerated in a rat toxicity study of 13 weeks duration, and no novel or increased toxicity was discerned. Target organ toxicities were consistent with known effects of both drugs, and generally associated with exaggerated pharmacological effects (predominantly of telmisartan). The observed toxicities were largely reversible.
- Genotoxicity, carcinogenicity, or reproductive toxicity studies were not submitted for the telmisartan/amlodipine combination. This is acceptable and consistent with TGA-adopted EU guidelines for combinations using previously approved components. As noted in the PI, Twynsta should not be used in pregnancy due to the known effects of angiotensin receptor blockers in the second and third trimesters of pregnancy.
- Both active substances have been approved and been on the market for many years. There is extensive nonclinical and clinical information available (for the individual components alone and in various dual combinations). Accordingly, there were no novel clinical safety concerns raised by the nonclinical data.
- There were no objections to the registration Twynsta tablets for the treatment of hypertension.

IV. Clinical Findings

Introduction

The program for registration consisted of five Phase I trials in healthy volunteers and five Phase III trials in patients with hypertension. All of these trials were completed at the time of this submission except for the open-label, long-term follow-up Phase III trial 1235.8.

These trials consisted of the following:

- three Phase I biopharmaceutic studies, including two bioavailability studies to confirm the bioequivalence of the proposed telmisartan/amlodipine fixed dose combination tablets with the respective single entity tablets and one food interaction study
- two Phase I drug-drug interaction studies to assess the potential pharmacokinetic interaction between telmisartan and amlodipine
- five Phase III studies to assess the efficacy and safety of the proposed telmisartan/amlodipine fixed dose combination tablets.

The objectives of the pivotal Phase III trials ***1235.5 and 1235.6*** and the supportive follow-up trials (***1235.7 and 1235.8***, respectively) were to demonstrate that treatment with the telmisartan/amlodipine (T/A) FDC in amlodipine non-responders is superior to continuation or up-titration of amlodipine monotherapy and to evaluate safety and tolerability of the FDC.

The pivotal Phase III trial ***1235.1*** had a 4x4 factorial design and was performed to confirm dose selection and assess the antihypertensive effects of the telmisartan/amlodipine combination as initial therapy. The need for an initial combination therapy in patients with moderate to severe hypertension or with high cardiovascular risk is described in the current TGA-approved EU guideline on the treatment of hypertension.[8] There are also more recently published European Medicines Agency (EMEA) draft guidelines on the clinical investigation

[8] EMEA, Committee for Medicinal Products for Human Use (CHMP), 23 June 2004. Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, CPMP/EWP/238/95 Rev 2.

of medicinal products in the treatment of hypertension (CPMP/EWP/238/95 Rev. 3). It was expected that these latest guidelines will be finalised in 2010.

The clinical trial program was planned and performed in accordance with the above relevant regulatory guidance and according to the Scientific Advice obtained from the EMEA on 26 January 2006. Among others, the following relevant issues for the clinical development were discussed in the Scientific Advice:

- The overall design of the nonresponder trials is in line with the nonresponder concept for development of FDCs. However, the inclusion of an additional arm where the dose of amlodipine should be increased to 10 mg in the 5 mg nonresponder trial was suggested in order to determine whether the combination products show any benefit in comparison to increasing the dose of amlodipine from 5 mg to 10 mg.
- The pivotal nonresponder trials as well as their open-label extension trials should preferably be performed with the T/A FDC. The other pivotal trial with a factorial design can be performed with the free combination. Bioequivalence of the free combination with the FDC needs to be demonstrated according to the TGA-adopted EU guideline on bioavailability and bioequivalence.[9]
- Provided that no substantial benefit of the combinations with 20 mg telmisartan can be demonstrated in the factorial design trial, development of only the FDCs of 40 mg or 80 mg telmisartan with amlodipine is acceptable.
- A 6 month period for safety assessment of the combination with safety data on 300-600 patients is acceptable, in accordance with the TGA-adopted EU guideline on fixed combination medicinal products.[7]

The factorial design trial 1235.1 evaluated first-line therapy based on hypertension guidelines issued in 2003 by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (Seventh Report) and the European Society of Cardiology/European Society of Hypertension (ESH/ESC) and in anticipation of more recent guidance from the ESH/ESC and new EU regulatory guidance (CPMP/EWP/238/95/95 Rev.3).

In CPMP/EWP/238/95 Rev. 2, at least the following is required if first-line therapy is claimed for a fixed low-dose combination:

1. Demonstration that each substance (component) has a documented contribution within the (fixed) combination:

It is necessary (but not sufficient) that the results of a valid clinical trial evaluating a fixed low-dose combination document a statistically significant and clinically relevant greater blood pressure lowering effect (for example > 2 mmHg with respect to seated diastolic blood pressure [sDBP]) than placebo, whereas the difference to each component (same sub-therapeutic low dose as in the fixed combination) given separately has to be at least statistically significant. In addition, the response rate on the low-dose fixed combination should exceed that on placebo by an amount which is statistically significant and clinically valuable.

2. Indication for a reduction of (dose-dependent) adverse drug reactions by the low dose fixed combination as compared to the components in the lowest approved dosages:

[9] EMEA. Committee for Proprietary Medicinal Products (CPMP), 26 July 2001. Note for Guidance on the Investigation of Bioavailability and Bioequivalence. CPMP/EWP/QWP/1401/98.

It is necessary (but not sufficient) that the blood pressure lowering effect of the low dose fixed combination is similar, that is, at least not inferior (for example decrease in mean sDBP < 2 mmHg lower than the active comparator) than those of the lowest approved dosage of each component. Moreover, there should be a trend towards better safety and response rate regarding the low-dose fixed combination as compared to each component administered at the lowest approved dosage.

In the draft guidelines CPMP/EWP/238/95/95 Rev.3 that are expected to be adopted in 2010 it is stated that the guidance on clinical investigation of medicinal products in the treatment of hypertension (CPMP/EWP/238/95 Rev. 1) refers to fixed combination products in a second-line indication and to a first line indication in sub-therapeutic doses of the two components. According to the guidance on fixed combination medicinal products (CPMP/EWP/240/95, 1996) in general an improvement of the benefit/risk assessment is required, either due to addition or potentiation of therapeutic activities or due to counteracting adverse reactions. In special instances a simplification of the therapy which improves patient compliance may justify the use of a fixed combination. The draft guidelines go on to state that initial therapy with two drugs should be considered when blood pressure is more than 20/10 mmHg above goal. The 2003 European Society of Hypertension/European Society of Cardiology (ESH/ESC) Guideline recommends that drug therapy should be started gradually either with monotherapy or with a "low dose" combination, irrespectively of initial blood pressure levels. There is no recommendation on special patient groups to be considered for a first line combination therapy. The term "low dose" as used in this ESH/ESC Guideline covers both sub-therapeutic and low therapeutic doses of the mono-components. This is in contrast to the *guidance on clinical investigation of medicinal products in the treatment of hypertension (CPMP/EWP/238/95 Rev. 1*) that explicitly refers to "sub-therapeutic" doses.

In the clinical development program the sponsor has designed the pivotal factorial study in accordance with the latest draft guidelines, and sub-therapeutic dose levels have not been included.

A pre-submission meeting was held between the sponsor, the EMEA, and rapporteur on 6 March 2009. Among others, agreement was reached on the following clinical issues:

- Results from the ongoing trial 1235.8 can be included in the submission dossier as an interim report. The final trial report and a comprehensive summary of the final results in relation to the relevance for the dossier are to be submitted with the applicant's response documentation.

Pharmacokinetics

Bioequivalence

Telmisartan/amlodipine FDC layered tablets were developed in the four dosage strengths: 80/10 mg, 80/5 mg, 40/10 mg and 40/5 mg. The two layers of the FDC can be considered as dose proportional among all strengths according to the TGA-adopted EU guidance.[9]

Tablets of the final formulation of telmisartan/amlodipine layered tablets were used in the Phase I clinical trials 1235.3, 1235.4 and 1235.12 and the efficacy/safety trials 1235.5-8. The pivotal factorial design Phase III study 1235.1 was performed using the US commercial single entity tablets telmisartan (Micardis; 20 mg, 40 mg and 80 mg manufactured without debossing) and amlodipine (Norvasc; 2.5 mg and 5 mg tablets, over-encapsulated for blinding purposes).

Bioequivalence of the single entity tablets used in study 1235.1 compared to the fixed dose combination tablets to be marketed was assessed in two Phase I studies with the highest and lowest dose strengths (1235.3 and 1235.4), and comparative dissolution studies with all four

dose strengths. Comparative dissolution testing of over-encapsulated versus non-encapsulated Norvasc tablets showed equivalency of the capsules and Norvasc tablets.

Specifically, the three biopharmaceutical Phase I clinical trials performed were:

- bioequivalence of the 40 mg telmisartan/5 mg amlodipine fixed dose combination tablet to the corresponding individual marketed tablets (Trial 1235.3)
- bioequivalence of the 80 mg telmisartan/10 mg amlodipine fixed dose combination tablet to the corresponding individual marketed tablets (Trial 1235.4)
- effect of a high-fat meal on bioavailability of the 80 mg telmisartan/10 mg amlodipine fixed dose combination tablet (Trial 1235.12)

Trials 1235.5 - 1235.8 all used the final, market entry formulation of the fixed dose combination tablets of telmisartan/amlodipine.

Trial 1235.3 - Bioequivalence of 40 mg telmisartan/5 mg amlodipine fixed dose combination compared with its monocomponents

This study, to demonstrate the bioequivalence of 40 mg telmisartan/5 mg amlodipine fixed dose combination versus commercial Micardis (telmisartan) tablets (40 mg) and commercial Norvasc (amlodipine besilate) tablets (5 mg) was also discussed in Section II. The results for $AUC_{0-\infty}$ and C_{max} are shown in Table 1.

For both telmisartan and amlodipine, the 90% confidence intervals (CIs) for both $AUC_{0-\infty}$ and C_{max} were contained in the bioequivalence acceptance range of 80-125%. Therefore bioequivalence of the fixed dose combination compared to the individual tablets can be concluded.

For telmisartan, median time to maximal plasma concentration (t_{max}) was 1.0 hour for the FDC and 1.5 hours for the individual tablets. $AUC_{0-\infty}$ was very similar in males and females, but C_{max} was 37-41% higher in the females compared to the males.

For amlodipine, t_{max} (6.0 hours) was identical for both treatments. $AUC_{0-\infty}$ was 12-16% higher and C_{max} was 27-28% higher in the female subjects compared to the males.

Trial 1235.4 - Bioequivalence of 80 mg telmisartan/10 mg amlodipine fixed dose combination compared with its monocomponents

This study, to demonstrate the bioequivalence of 80 mg telmisartan/10 mg amlodipine fixed dose combination vs commercial Micardis (telmisartan) tablets (80 mg) and commercial Norvasc (amlodipine besilate) tablets (10 mg) was also discussed in Section II. The results for $AUC_{0-\infty}$ and C_{max} are shown in Table 2.

For both telmisartan and amlodipine, geometric mean plasma concentration-time profiles were closely similar between the FDC and individual tablet treatments. For telmisartan, median t_{max} was practically identical for both treatments (1.0 hour). $AUC_{0-\infty}$ was 26-39% higher and C_{max} was 85-104% higher in the female subjects compared to the males.

For amlodipine, median t_{max} was identical for both treatments (6.02 hours). $AUC_{0-\infty}$ was 14-15% higher and C_{max} was 21-22% higher in the female subjects compared to the males.

For both telmisartan and amlodipine, the 90% CIs for both $AUC_{0-\infty}$ and C_{max} were contained in the bioequivalence acceptance range of 80-125%. Therefore bioequivalence of the fixed dose combination compared to the individual tablets can be concluded. The fixed dose combination of telmisartan 80 mg and amlodipine 10 mg is bioequivalent to the individual marketed tablets administered together.

Trial 1235.12 - Influence of food on the bioavailability of 80 mg telmisartan/10 mg amlodipine fixed dose combination

This study, to investigate the effect of food intake on the bioavailability of a fixed dose combination of 80 mg telmisartan/10 mg amlodipine following a high fat breakfast was also discussed in Section II. The results for $AUC_{0-\infty}$ and C_{max} are shown in Table 3.

For telmisartan, geometric mean plasma concentration-time profiles after a high fat meal showed a markedly lower and slightly later peak compared to the fasted state, indicating delayed absorption. Median t_{max} (range) increased from 0.98 (0.5–2.5) hours when fasted to 2.0 (0.5 – 12) hours after food, but there was no effect on terminal half-life. The high-fat meal had a greater effect in reducing C_{max} and $AUC_{0-\infty}$ in the female subjects compared to the males, and after food C_{max} and $AUC_{0-\infty}$ were higher in males compared to females.

For amlodipine, $AUC_{0-\infty}$ and C_{max} were minimally increased after the high-fat meal and t_{max} was slightly reduced. Median t_{max} (range) decreased from 6.0 (2.0-10.1) hours when fasted to 5.1 (1.0-12) hours after food. $AUC_{0-\infty}$ and C_{max} were higher for females compared to males in both the fed and fasted states.

The 90% CI were not included in the acceptance range of 80-125% and therefore a lack of food effect on bioavailability of telmisartan could not be concluded. In a previous study performed with telmisartan the effect of food on telmisartan pharmacokinetics was determined for 40 mg and 160 mg doses, and was found to be dose dependent. The present results with 80 mg telmisartan are very similar to those observed with the 160 mg dose, and are more pronounced than those observed with the 40 mg dose in Study 502.113.

The 90% CIs of the geometric mean (high-fat meal/fasted) ratios for $AUC_{0-\infty}$ and C_{max} were included in the acceptance range of 80-125% for amlodipine but not for telmisartan. Therefore a lack of food effect on pharmacokinetics can be concluded for amlodipine but not for telmisartan.

Absorption

Telmisartan

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in $AUC_{0-\infty}$ of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food. The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. C_{max} and, to a lesser extent, the AUC increase disproportionately at doses above 40 mg.

Amlodipine

After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food.

Distribution

Telmisartan

Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (Vd_{ss}) is approximately 500 l.

Amlodipine

Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.

Metabolism

Telmisartan

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Amlodipine

Amlodipine is extensively (about 90%) converted to inactive metabolites *via* hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Elimination

Telmisartan

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. C_{max} and AUC increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy. After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cl_{tot}) is high (approximately 1,000 mL/min) compared with hepatic blood flow (about 1,500 mL/min).

Amlodipine

Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Special Populations

Gender effects

Telmisartan

Differences in plasma concentrations were observed, with C_{max} and AUC being approximately 3- fold and 2-fold higher, respectively, in females compared to males.

Elderly patients

Telmisartan

The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.

Amlodipine

Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%, and a lower initial dose may be required.

Patients with renal impairment

Telmisartan

In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis.

Telmisartan is highly bound to plasma protein in renal-insufficient patients and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Amlodipine

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Patients with hepatic impairment

Telmisartan

Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100 %. The elimination half-life is not changed in patients with hepatic impairment.

Amlodipine

Patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%.

Paediatric Patients

Amlodipine

Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Heart failure

Amlodipine

Patients with heart failure have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%.

Steady State Pharmacokinetics

Trial 1235.2 - Pharmacokinetics of repeated oral doses of 80 mg telmisartan (Micardis) at steady state alone and in combination with repeated oral doses of amlodipine 10 mg (Norvasc) at steady state - a two-way crossover, open, randomised design study

This study was an open-label, multiple dose, randomised, two-way, two sequence crossover design. Thirty eight healthy male or female Caucasian volunteers, age 18 to 50 years, with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were entered.

Steady state plasma concentrations for telmisartan were achieved at the latest on Day 6 and for amlodipine on Day 7. Geometric mean area under the plasma concentration time curve at steady state over a uniform dosing period τ ($AUC_{\tau,ss}$) of telmisartan for the 36 subjects who received the entire dosage regimen (18 men and 18 women) was 1020 ng.h/mL (intersubject mean coefficient of variance [gCV] 74%) when administered alone and 999 ng.h/mL (intersubject gCV 95%) with amlodipine. Geometric mean maximal plasma concentration at

steady state over a uniform dosing period τ ($C_{max,ss}$) was 272 ng/mL (intersubject gCV 105%) for telmisartan alone and 242 ng/mL (intersubject gCV 118%) for telmisartan with amlodipine. A higher systemic exposure to telmisartan was observed in the female subjects compared to the males (77% higher for $AUC_{\tau, ss}$ and 97% higher for $C_{max,ss}$ without amlodipine) but this is consistent with previously reported results.

The total and peak systemic exposure achieved for amlodipine ($AUC_{\tau, ss}$ = 300 ng.h /mL, intersubject gCV 34.6% and $C_{max,ss}$ = 15.8 ng/mL, gCV 33.2%) was comparable with previously published data and was therefore adequate to ensure a valid assessment of its interaction potential towards telmisartan. The geometric mean ratios and 90% confidence intervals of $AUC_{\tau, ss}$ and $C_{max,ss}$ for telmisartan with (T = test) and without amlodipine (R = reference) are shown in Table 5.

Table 5: Trial 1235.2 - Geometric mean ratios and 90% confidence intervals of $AUC_{\tau, ss}$ and $C_{max,ss}$ for telmisartan with (T = test) and without amlodipine (R = reference)

Parameter	**T/R ratio**	**90% CI**	
N = 36		lower limit	upper limit
	[%]	[%]	[%]
$AUC_{\tau,ss}$	97.64	89.49	106.53
$C_{max,ss}$	88.98	76.317	103.745

The confidence interval for the $AUC_{\tau,ss}$ ratio was within the pre-specified no-effect acceptance limits of 80–125%, and the confidence interval for the $C_{max,ss}$ ratio was within the pre-specified no-effect limits of 75–133%. The latter were defined to be wider than for $AUC_{\tau,ss}$ because telmisartan is known to be a highly variable drug with respect to intrasubject variability of C_{max}, but also has a wide therapeutic window. The high intrasubject variability of telmisartan C_{max} was confirmed in the present study (40.0%) whereas for AUCτ,ss it was only 22.1%. It can be concluded that there is no clinically significant change in systemic exposure to telmisartan 80 mg on coadministration of amlodipine 10 mg after dosing both medications to steady state and that there is no relevant drug-drug interaction with regard to the effect of amlodipine on telmisartan.

Trial 502.126 - Pharmacokinetics of repeated oral doses of 10 mg amlodipine daily and of 10 mg amlodipine and 120 mg telmisartan daily in a cross-over randomised open study in healthy subjects

This study was an open, randomised, two way crossover trial with a wash out period of 13 days between the two treatments, in 12 healthy male volunteers.

Pharmacokinetic results are summarised in Table 6. Comparison of the ratio of amlodipine pharmacokinetic parameters with and without telmisartan to the acceptance range 0.8–1.25 showed bioequivalence for AUC_{ss} and $C_{max,ss}$ of amlodipine.(see Table 7). It can be concluded that telmisartan did not alter the pharmacokinetics of amlodipine and that there is therefore no drug-drug interaction.

Table 6: Trial 502.126 – Pharmacokinetic results

parameter	units	amlodipine without telmisartan	amlodipine with telmisartan	telmisartan (with amlodipine)
C_{max}	ng/ml	5.4	5.55	311
$C_{max,ss}$	ng/ml	17.7	18.7	494
t_{max}	h	7	8	1.25
$AUC_{0.24h}$	ng·h/ml	90.5	95.8	1000
AUC_{ss}	ng.h/ml	331	352	1590
$t_{1/2}$	h	56	52	19
Ae	%	8	9.4	--

(geometric mean values except t_{max}, for which the median is given, Ae = urinary excretion)

Table 7: Trial 502.126 - Comparison of the ratio of amlodipine pharmacokinetic parameters with and without telmisartan

parameter (amlodipine) N = 12	geometric mean ratio with/without telmisartan	Lower 90% confidence limit	Upper 90% confidence limit
$C_{max,ss}$	1.06	0.97	1.14
AUC_{ss}	1.06	0.98	1.16

Evaluator's conclusions on biopharmaceutics and pharmacokinetics

Comparability of the to-be-marketed T/A FDC tablets and the individual tablets of single entity tablets used in the Phase III pivotal efficacy study 1235.1 was demonstrated in Study 1235.3 demonstrating bioequivalence between the lowest proposed FDC dose strength (T40/A5) and commercial Micardis (telmisartan) tablets (40 mg) or commercial Norvasc (amlodipine) tablets (5 mg). Study 1235.4 demonstrated bioequivalence between the highest proposed FDC dose strength (T80/A10) and commercial Micardis (telmisartan) tablets (80 mg) or commercial Norvasc (amlodipine) tablets.

The effect of a high-fat breakfast on the bioavailability of the proposed highest dose strength of the fixed dose combination (80 mg telmisartan / 10 mg amlodipine) was investigated in Study 1235.12. The results of this study showed a food effect on the bioavailability of the telmisartan component of the telmisartan/amlodipine FDC tablet. The telmisartan formulation used in the telmisartan layer of the telmisartan/amlodipine bilayered FDC tablet is the same as that used in Micardis (telmisartan) tablets. For telmisartan in Study 1235.12, the geometric mean fed to fasted ratio (90% CI) was 75.7% (71.2–80.5%) for $AUC_{0-\infty}$ and 39.9% (33.1–48.1%) for C_{max}. Thus, the high-fat meal decreased telmisartan $AUC_{0-\infty}$ by 24.3% and C_{max} by 60.1%.

Trial 1235.2 was an open-label, randomised, two-way crossover study in 38 healthy subjects to compare the steady-state pharmacokinetics of the highest telmisartan dose (80 mg) alone

and with amlodipine (10 mg). The 90% CIs of the geometric mean ratios of telmisartan steady-state AUC and C_{max} with and without amlodipine were within the pre-specified no-effect boundaries of 80–125% for AUC and 75–133% for C_{max}. Therefore, the trial showed that amlodipine did not alter the pharmacokinetics of telmisartan at steady state.

An earlier trial (502.126) demonstrated that telmisartan (120 mg) had no effect on the steady state pharmacokinetics of amlodipine (10 mg). In conclusion, the two interaction studies demonstrate that the pharmacokinetics of amlodipine at steady state are not altered by the presence of telmisartan and vice-versa. There is no significant drug-drug interaction between the two substances.

Pharmacodynamics

The clinical pharmacodynamic characteristics of telmisartan and amlodipine have been fully described for the individual telmisartan and amlodipine products. No new pharmacodynamic data were presented for evaluation.

Efficacy

Introduction

The clinical program for evaluating the efficacy of the T/A FDC included 5 multicentre clinical trials:

- 1235.5 and 1235.6: Pivotal non-responder trials for second-line indication
- 1235.7 and 1235.8: Supportive follow-up trials for second-line indication
- 1235.1: Pivotal trial with 4 × 4 factorial design for first-line indication and dose finding

In trials 1235.5, 1235.6, 1235.7, and 1235.8, patients were treated with one of the four telmisartan and amlodipine FDCs that are intended for marketing. The dose strengths of telmisartan and amlodipine in these FDCs are indicated as T40/A5, T40/A10, T80/A5, and T80/A10. In trial 1235.1, patients were randomised to free combinations of telmisartan and amlodipine tablets. The dose strengths of telmisartan and amlodipine in these free combinations are indicated as T40+A5, T40+A10 etc. in order to distinguish them from the T/A FDCs used in trials 1235.5–1235.8. Bioequivalence of the free combinations and the TA/FDCs was demonstrated in trials 1235.3 and 1235.4.

Main (pivotal) studies - Trials 1235.5, 1235.6 and 1235.1

Trial 1235.5

This was an eight-week randomised, four-arm, double-blind study to compare the efficacy and safety of combinations of telmisartan 40 mg + amlodipine 5 mg versus telmisartan 80 mg + amlodipine 5 mg versus amlodipine 5 mg monotherapy versus amlodipine 10 mg monotherapy in patients with hypertension who fail to respond adequately to treatment with amlodipine 5 mg monotherapy

The primary objectives were: (a) to demonstrate that the FDC T40/A5 or the FDC T80/A5 is superior over A5 in reducing BP at 8 weeks, (b) to demonstrate that the FDC T40/A5 or the FDC T80/A5 is not inferior vs A10 in reducing BP at 8 weeks, and (c) to demonstrate that the incidence of oedema is lower for the pooled treatment groups T40/A5 and T80/A5 than for the A10 treatment group. These objectives were tested in hypertensive patients who failed to respond adequately but tolerated A5, that is, who had a trough sDBP ≥90 mmHg after a 6-week treatment with A5.

For non-inferiority tests, the non-inferiority margin was 2 mmHg, in line with the TGA-adopted EU guidance.[8]

Trial 1235.5 had a non-responder design in patients with uncontrolled hypertension, defined as sDBP ≥95 mmHg if patients were on antihypertensive treatment within the month prior to giving informed consent, or sDBP≥100 mmHg if they were treatment -naïve within the month prior to giving informed consent. Patients who tolerated but failed to respond adequately to 6 weeks of open-label treatment with A5 were randomised in a 1:1:1:1 ratio to an 8-week triple-dummy treatment with T40/A5, T80/A5, A5, or A10. Trough sBP was measured approximately 24 hours post-dose at each visit.

Trial 1235.6

This was an eight-week randomised, three-arm, double-blind study to compare the safety and efficacy of the combination of telmisartan 40 mg + amlodipine 10 mg versus telmisartan 80 mg + amlodipine 10 mg versus amlodipine 10 mg monotherapy in patients with hypertension who fail to respond adequately to treatment with amlodipine 10 mg monotherapy.

The primary objective was to show that the FDC T40/A10 or the FDC T80/A10 was superior in reducing BP at 8 weeks compared with A10 monotherapy. This objective was assessed in hypertensive patients who failed to respond adequately to A10, that is, who had a trough sDBP ≥90 mmHg after a 6-week treatment with A10.

Patients who tolerated but failed to respond adequately to 6 weeks of open-label treatment with A10 (preceded by 2 weeks with A5) were randomised in a 1:1:1 ratio to an 8-week double-dummy treatment with T40/A10, T80/A10, or A10. Trough seated BP was measured 20 to 30 hours post-dose at each visit.

Trial 1235.1

This was a randomised, double-blind, double-dummy, placebo-controlled, 4x4 factorial design trial to evaluate telmisartan 20, 40 and 80 mg tablets in combination with amlodipine 2.5, 5 and 10 mg capsules after eight weeks of treatment in patients with Stage I or II hypertension, with an ambulatory blood pressure monitoring (ABPM) sub-study.

The primary objective of this trial was to demonstrate that for both active therapies of telmisartan and amlodipine there existed an overall dose response thereby showing that combinations of telmisartan and amlodipine were more effective in reducing DBP than each of the respective monotherapies in patients with Stage 1 or 2 hypertension.

This 8 week trial was conducted in 1461 adult male and female patients. In terms of inclusion criteria hypertension was defined by a mean seated cuff diastolic blood pressure of ≥95 mmHg and ≤119 mmHg at Visit 3. In order for patients to qualify after only three weeks of run-in treatment, the mean seated cuff diastolic blood pressure had to be≥100 mmHg and ≤119 mmHg.

Patients were randomised into a 4×4 factorial design treatment allocation as shown in Table 8 below. The randomisation scheme assigned more patients (3:1 ratio) to the 8 treatment groups of primary interest (telmisartan 40, 80 mg/day; amlodipine 5, 10 mg/day, telmisartan/amlodipine combinations of 40+5, 40+10, 80+5, 80+10 mg) than to the 8 other groups. A total of 789 patients received one or more doses of telmisartan with amlodipine administered as single entity tablets.

Table 8: Number of patients per treatment group in trial 1235.1

	Placebo	Amlodipine 2.5 mg	Amlodipine 5 mg	Amlodipine 10 mg
Placebo	46	50	140	129
Telmisartan 20 mg	42	44	46	44
Telmisartan 40 mg	130	47	143	129
Telmisartan 80 mg	135	48	146	142

Inclusion/exclusion criteria

For trials 1235.5 and 1235.6 at screening, patients had to have a diagnosis of essential hypertension with inadequately controlled BP; inadequate control was defined as sDBP≥95 mmHg if on antihypertensive treatment or≥100 mmHg if treatment naïve. T rial 1235.5 was performed in Western Europe, Asia, Canada, and South Africa; trial 1235.6 was performed in Western and Eastern Europe and Australasia.

For study 1235.5 and 1235.6 inclusion criteria included failure to respond adequately to 6 weeks of treatment with A5 monotherapy (defined as sDBP≥90 mmHg at 6 weeks [Visit 3])

For trial 1235.1 patients had to have a diagnosis of essential hypertension defined by a mean sDBP of ≥95 mmHg and ≤119 mmHg at Visit 3. In order for patients to qualify after only three weeks of run-in treatment, sDBP had to be ≥100 mmHg and ≤119 mmHg

There were numerous exclusion criteria in all three trials which conformed to the pattern of similar trials.

Efficacy endpoints

Primary endpoints

The primary efficacy variable in all 5 efficacy trials was trough (24 hours post-dose) sDBP at the last visit during the treatment phase. In the randomised double-blind trials 1235.5, 1235.6, and 1235.1 the change from baseline in trough sDBP was the primary endpoint.

In the open-label follow-up trials 1235.7 and 1235.8, the proportion of patients achieving DBP control (defined as mean trough sDBP <90 mmHg) was the primary endpoint.

Oedema is a known dose-dependent side effect of amlodipine treatment. The occurrence of oedema may reduce patient compliance and may even lead to discontinuation. The incidence of oedema was pre-specified as a primary efficacy endpoint in trial 1235.5 and included in the pre-specified hierarchical testing sequence in the trial-related analyses.

Secondary endpoints

The secondary efficacy endpoints related to auscultatory seated BP measurements were:

- The change from baseline in trough sDBP at individual visits during the treatment phase
- The change from baseline in trough sSBP at individual visits and the last visit during the treatment phase
- The proportion of patients achieving DBP control (defined as trough sDBP<90 mmHg, sDBP<80 mmHg) at individual visits and the last visit during the treatment phase
- The proportion of patients achieving SBP control (defined as trough sSBP<140 mmHg, sSBP<130 mmHg) at individual visits and the last visit during the treatment phase

- The proportion of patients achieving DBP response (defined as trough sDBP<90 mmHg or trough sDBP reduction from baseline≥10 mmHg) at individual visits and the last visit during the treatment phase
- The proportion of patients achieving SBP response (defined as trough sSBP<140 mmHg or trough sSBP reduction from baseline≥20 mmHg) at individual visits and the last visit during the treatment phase
- The proportion of patients in each of the following trough sBP categories at individual visits and the last visit during the treatment phase according to the European Hypertension Guideline 2007 (Note: In the trial reports, the definitions according to JNC7 guidance were used):
    - Optimal: SBP <120 mmHg and DBP <80 mmHg
    - Normal: SBP <130 mmHg and DBP <85 mmHg but not 'optimal'
    - High-normal: SBP <140 mmHg and DBP <90 mmHg but not 'normal'
    - Grade 1 hypertension(mild): SBP <160 mmHg and DBP <100 mmHg but not 'high-normal'
    - Grade 2 hypertension (moderate): SBP <180 mmHg and DBP <110 mmHg but not 'Grade 1 hypertension'
    - Grade 3 hypertension (severe): SBP ≥180 mmHg or DBP ≥110 mmHg

The secondary efficacy endpoints related to ABPM measurements in trial 1235.1 were:

- Change from baseline in the 24-hour ABPM mean (relative to dosing time) for DBP and SBP
- Hourly mean profiles (relative to dosing time) for DBP and SBP

Statistical Methods and Sample Size

Continuous variables were described by the following descriptive statistics: number of patients (N), mean, standard deviation (sd), standard error (se), range (minimum, maximum), and 95% confidence interval (CI). For least square means (adjusted means), the se and 95% CI were given. In the follow-up trials 1235.7 and 1235.8, baseline information was taken from the preceding trial (trial 1235.5 and 1235.6, respectively).

Study 1235.1

Previous studies with telmisartan in hypertensive patients suggested that the standard deviation of changes from baseline in sDBP may be as much as 8.5 mmHg. From simulations of the analysis of covariance (ANCOVA) including the main effects of telmisartan and amlodipine, using expected treatment effects and utilising the estimate of 8.5 mmHg for the standard deviation of the results, it was shown that with the sample sizes of either 120 or 40 patients there was virtually 100% chance of finding a significant ($p \leq 0.05$) dose response due to both telmisartan and amlodipine. From further simulations performed on the full ANCOVA statistical model (including the telmisartan X amlodipine interaction), there was a 71.6% chance of not finding statistical significance ($p>0.10$) for the treatment-by-treatment interaction term. If patients treated with placebo are excluded from this full ANCOVA the probability of not finding statistical significance ($p>0.10$) for the treatment-by-treatment interaction term increases to 87.8%. From the above simulation of the full comparisons of the treatment effects for the four key treatment combinations utilising the Hochberg procedure to the respective individual components resulted in powers to detect significant differences of a combination treatment over both of its individual components ranging from 82.8-87.6%.

Study 1235.5

In a filter-design study of non-responders to the FDC telmisartan80/hydrochlorothiazide12.5 (T80/H12.5), the standard deviation (sd) of the change from baseline in the trough sDBP in patients randomised to T80/H12.5 was 6.4 mmHg and for the FDC T80/H25, the sd was 6.8 mmHg. Using an estimate of 6.6 mmHg, a sample size of 240 evaluable patients per treatment group would have approximately 90% power to detect a 2.0 mmHg difference between treatments in the reduction from baseline in trough sDBP (2-sided, alpha=0.05). Likewise, 240 evaluable patients deliver 90% power to demonstrate non-inferiority if both treatments are equal. To achieve this number of evaluable patients, it was estimated that approximately 2024 patients would need to be enrolled in the study to attain the required 960 evaluable patients. With this sample size, the study was powered to detect a difference in trough sDBP. As part of the primary analysis, oedema occurrence rates were compared. To ensure that the trial would have suitable power to detect a difference in these rates, oedema incidences from recent studies were evaluated. The oedema incidence for treatment with A10 was therefore expected to be 10.3% and 2.1% for the combination therapies. Using these estimates and the treatment group size of 240, the power would be approximately 96% (2-sided, alpha=0.05).

Study 1235.6

As described above in a previous non-responder design study the standard deviation (sd) of the change from baseline in the trough sDBP in patients randomised to T80/H12.5 was 6.4 mmHg and for the FDC T80/H25, the sd was 6.8 mmHg. Using an estimate of 6.6 mmHg, a sample size of 240 evaluable patients per treatment group would have approximately 90% power to detect a 2.0 mmHg difference between treatments in the reduction from baseline in trough sDBP (2-sided, alpha=0.05).

Study 1235.7

This was an open-label follow-up trial. All patients who were randomised to and completed the preceding trial 1235.5 were eligible for inclusion. The planned number of evaluable patients from 1235.5 was 1012, and therefore this was the maximum number of patients possible in this open-label trial.

Study 1235.8

This was an open-label follow-up trial. All patients who completed the preceding trial were eligible for inclusion. It was expected that approximately 90% of patients who completed study 1235.6 would enter this open-label trial. The planned number of randomised patients in 1235.6 was 756, and accordingly the number of patients initially planned to be included in this trial was 680. However, 949 patients were actually randomised in the 1235.6 study and so the planned number for patients to be randomised for this open-label study was changed to 900.

Handling of missing values

In the case of categorical or categorised variables, frequency tables with percentages were displayed. Missing data were displayed as a separate category ‘Missing’. The last observation carried forward (LOCF) principle was applied to all efficacy variables, that is, if the BP measurement at the end of trial was missing the last available value on the same treatment was used instead. However, baseline and non-trough values were not carried forward. If only partial dates were available, the 15th of that month was used for a missing day and the 1st July for a missing day and month.

Analysis populations

Double-blind trials 1235.5, 1235.6 and 1235.1

The full analysis set (FAS) used for trials 1235.5, 1235.6 and 1235.1 comprised all randomised patients who had taken at least one dose of double-blind study medication and for whom a baseline and at least one post-baseline trough BP measurement were available.

Within trial 1235.1, analyses were also performed on two subsets of patients with hypertension that would potentially benefit most from initial therapy with 2 antihypertensive medications:

- Patients with DBP ≥100 mmHg at baseline (DBP100)
- Patients with DBP ≥100 mmHg or SBP ≥160 mmHg at baseline (Grade 2/3)

The DBP100 subset was prospectively defined for the trial analysis and the Grade 2/3 subset was analysed post hoc. Efficacy in trial 1235.1 was mainly based on changes in DBP since patients were enrolled into the trial according to their baseline DBP and because DBP was the primary endpoint. As such, the main focus for trial 1235.1 in this report will be on the FAS and DBP100 results.

The analysis set for patients who participated in the ABPM substudy of trial 1235.1 had valid ABPM values at both baseline and following treatment with target therapy. All ABPM analyses were based on hourly means. ABPM values were regarded as being invalid if more than 3 consecutive hourly means were missing, or if more than 6 hourly means were missing during the 24-hour dosing period in total.

Patient disposition

Trials 1235.5 and 1235.6

A total of 2719 patients were treated with at least one dose of open-label run-in medication in the two non-responder trials: 1363 patients in trial 1235.5 (A5 for 6 weeks) and 1356 patients in trial 1235.6 (A5 for 2 weeks, followed by A10 for 6 weeks). The majority of patients (2047, 75.3%) completed the run-in phase, were not adequately controlled on amlodipine monotherapy, and were randomised to the double-blind treatment phase: 1098 (80.6%) in trial in 1235.5 and 949 (70.0%) in trial 1235.6. The most common reasons for discontinuation in the run-in phase were violation of inclusion or exclusion criteria (16.9%) followed by adverse effects (AEs) (5.0%). The proportion of patients who discontinued during the run-in phase in trial 1235.6 was higher than in trial 1235.5 (30.0% vs 19.4%), mainly because of higher frequencies of discontinuations due to violations of inclusion/exclusion criteria (19.1% vs 14.7%) and AEs (7.4% vs 2.6%). Note that for many of the patients who were not randomised, attaining a DBP <90 mmHg was the inclusion criterion violated and it was expected that there would be more such patients in a trial with A10 versus A5 as the run-in medication.

A total of 1978 patients were randomised and treated in the double-blind phase of the two trials (FAS): 1057 in trial 1235.5 and 921 in trial 1235.6. The majority of patients completed their planned 8 weeks of treatment. Discontinuation rates were low and similar: 2.7% (29/1057) patients in trial 1235.5 and 2.9% (27/921) patients in trial 1235.6. The most common reason for premature discontinuation in both trials was the occurrence of AEs: 1.5% (16) vs 1.6% (15) patients, respectively. The majority of these patients discontinued due to AEs that were not related to worsening of the study disease or other pre-existing diseases.

In trial 1235.5, the discontinuation rate in the T40/A5 group (0.4%) was lower than in the 3 other treatment groups (A5 3.1%, A10 4.6%, T80/A5 3.0%). In trial 1235.6, discontinuation

rates ranged from 1.9% in the T80/10 group to 3.9% in the T40/A10 group. The pattern of discontinuations was generally similar across the treatment groups. However, in trial 1235.5, the proportion of discontinuations due to AEs was higher in group A10 (4.2%) than in the other treatment groups (A5 1.2%, T40/A5 0.4%, T80/A5 0.4%).

Trial 1235.1

Most patients in the FAS and in the DBP100 subset completed their planned 8 weeks of treatment. The discontinuation rate for the FAS population was 6.7% (95/1423 patients). The most common reasons for discontinuation were administrative and the occurrence of AEs, occurring in 2.7% and 2.2% of the population, respectively. Disposition was similar for the DBP100 subset.

FAS

The pattern of patient disposition was generally similar across pooled treatment groups. Across the pooled active treatments, the rate of discontinuation due to AEs was similar at approximately 2%.

The pattern of patient distribution for the FAS had between 3.9% and 15.2% of patients in each treatment group prematurely discontinuing treatment. The placebo group, not unexpectedly, had the highest discontinuation rate. For patients receiving telmisartan (T40 or T80), the largest discontinuation rate due to AEs was always in the treatment group receiving telmisartan and concomitant high-dose amlodipine (T40+A10 and T80+A10).

DBP100

The pattern of patient disposition was generally similar across pooled combination and monotherapies, and also similar to that previously presented for the FAS. In the placebo group, 17% of patients discontinued treatment prematurely compared with rates ranging from 5.6% to 7.2% in the pooled active treatments.

The pattern of patient disposition, when examined by key combination treatment groups and respective monotherapies, for the DBP100 subset show that 2.0% to 17.1% prematurely discontinued treatment. The placebo treatment group (T0+A0) had the highest proportion of patients discontinuing treatment. A small and inconsistently varying percentage of patients discontinued due to administrative reasons. As noted above, more patients generally discontinued for AEs in the groups receiving high-dose amlodipine (10 mg) than in the other treatment groups.

Grade 2/3 subset

In the Grade 2/3 subset, 7% of the patients discontinued treatment prematurely. The majority of patients discontinued due to AEs and administrative reasons, most commonly consent withdrawn. The pattern of patient distribution was similar to that of the FAS.

Demographics and baseline data

Trials 1235.5 and 1235.6

The majority of patients in the FAS of trials 1235.5 and 1235.6 were under 65 years, with a slightly lower mean (sd) age across all treatment groups in trial 1235.5 than in trial 1235.6: 54.2 (10.6) vs 56.5 (9.9) years. The majority of patients were male, with a slightly higher proportion of males in trial 1235.5 than in trial 1235.6: 62.4% vs 55.2%. Patients displayed a high mean (sd) BMI in both trials: 29.3 (5.3) kg/m² in trial 1235.5 and 30.1 (4.6) kg/m² in trial 1235.6. Almost all of the patients were non-Black. Within each trial, demographic characteristics were generally comparable across the treatment groups.

Trial 1235.1

FAS and DBP100

The mean age of patients comprising the FAS was 53.0 years. The majority of patients (85.8%) were <65 years of age and half (50.5%) were male. The majority of patients (79.4%) were White, 16.3% were Black, and the remaining 4.3% were Asian. Demographics for the DBP100 subset were similar to those for the FAS.

FAS

Demographic characteristics were generally similar across pooled combined treatments with approximately half of the patients being male and the majority being White and less than 65 years of age. There were however, a somewhat higher proportion of males (63.0%) and whites (87.0%) in the placebo group than in the pooled active treatments. No notable differences were observed in weight, height, or BMI across the combined treatment groups

DBP100

Patient groups were well balanced for demographic characteristics. As with the FAS, a higher proportion of patients in the placebo group were white or male compared with the pooled combination and monotherapies. The number of patients in the placebo group was smaller; perhaps accounting for these differences. No notable differences were observed in weight, height, and BMI across the pooled combination and monotherapies.

Patient demographics for the DBP100 subset were generally similar across the key combination treatment groups and respective monotherapies with few exceptions. There were no notable differences across these groups for age or weight/height/BMI.

Most patients within each individual treatment group were less than 65 years of age and white. With the exception of the placebo (71% male/29% female) and the T80+A0 monotherapy (38% male/62% female) treatment groups, the proportion of males to females was well-balanced in individual treatment groups.

Grade 2/3 subset

Patient demographics for the Grade 2/3 subset were generally similar to the FAS and DBP100 subsets. Overall, there were no notable differences in the demographic profile of the Grade 2/3 subset from those described for the FAS and the DBP100 subset when examined by key combinations and respective monotherapy treatment groups.

Baseline disease characteristics in trials 1235.5 and 1235.6

Overall, several differences were apparent between the non-responder trials 1235.5 and 1235.6 with regard to the baseline characteristics of the underlying hypertension. In general, patients in trial 1235.5 had less severe baseline hypertension than patients in trial 1235.6. The mean (sd) duration of hypertension prior to trial entry was lower in trial 1235.5 than in trial 1235.6: 5.9 (7.4) vs 8.1 (7.4) years, respectively. Furthermore, the overall proportion of patients who had taken previous antihypertensive treatment was lower in trial 1235.5 (67.0%) than in trial 1235.6 (86.2%). Although the majority of patients in both trials had Grade 1 hypertension at baseline, the percentage was lower in trial 1235.5 (64.8%) than in trial 1235.6 (75.7%). These findings can be expected because the patients in trial 1235.5 failed to respond to 5 mg/day amlodipine (A5 monotherapy) during the 6-week run-in phase whereas patients in trial 1235.6 failed to respond to the maximum registered amlodipine dose of 10 mg/day (A10 monotherapy). Within each trial, the characteristics of the underlying hypertension were well balanced across the treatment groups.

Baseline disease characteristics in trial 1235.1

FAS and DBP100

No relevant differences were noted between the FAS and the DBP100 subset with regard to duration of hypertension, previous antihypertensive treatment, or DBP and SBP at baseline. Corresponding baseline disease data for the DBP100 subset was similar to that of the FAS. Based on the definition of the patient subset, the mean DBP and SBP readings at randomisation were slightly higher for the DBP100 subset than for the FAS.

FAS

When examined by pooled combination and monotherapies, baseline data for hypertension were generally similar, with most patients having hypertension for 1 to 5 years. Approximately one-third of patients had received 1 or 2 previous antihypertensive treatments and approximately 10% had received 3 or more previous antihypertensive treatments. Baseline data for hypertension were generally similar across the key combination treatment groups and respective monotherapies, including placebo.

DBP100

Baseline disease data for the DBP100 subset was similar to that of the FAS. As would be expected, the mean DBP and SBP readings at randomisation were slightly higher for the DBP100 subset than for the FAS. No notable differences, distinct from those presented for the FAS, were observed in the DBP100 subset.

Baseline characteristics in trials 1235.5 and 1235.6

Less than half of the patients in the FAS of trials 1235.5 and 1235.6 had a history of smoking (current or past): 37.7% in trial 1235.5 and 32.4% in trial 1235. About 60% of the patients reported use of alcohol (65.4% in trial 1235.5 vs 59.4% in trial 1235.6) and about 40% had a BMI ≥30 kg/m² (37.9% vs 45.5%). About 10% of patients were diabetics (9.0% vs 12.8%) and about 5% were renally impaired (3.6% vs 8.3%). About 20% of patients took concomitant NSAIDs or COX-2 inhibitors (18.4% vs 20.0%). Within each trial baseline characteristics were well balanced across the treatment groups. In trial 1235.5, however, the proportion of patients with a BMI ≥30 kg/m² in the A10 group (32.2%) was lower than in the T80/A5 group (43.5%).

Baseline characteristics factors in trial 1235.1

FAS and DBP100

Baseline characteristics were similar for the FAS and the DBP100 subset. Slightly more than half of the patient population had BMI ≥30 kg/m² and slightly less than half reported smoking (either current or past) and/or alcohol use.

FAS

Baseline characteristic data were generally similar across pooled combination treatments. Overall, the populations were well-balanced for each baseline characteristic across the key combination treatment groups and respective monotherapies. There were no notable differences across these groups for smoking history or alcohol history. Diabetic patients comprised ≤19% and renally impaired patients comprised ≤9% of the population in any of the key combination treatment groups and respective monotherapy groups.

DBP100

Overall, baseline characteristic data were generally similar across the pooled combination and monotherapies. The populations were well-balanced for each baseline characteristic across

the key combination treatment groups and respective monotherapies and similar to the FAS results. In the DBP100 subset there were no notable differences across these groups for smoking history or alcohol history.

Concomitant diseases

In trial 1235.5, 82.4% of patients reported one or more concomitant diseases. The most common System Organ Classes (SOCs) (≥20.0% patients overall) were *Metabolism and Nutrition Disorders* (40.7%) and *Musculoskeletal and Connective Tissue Disorders* (28.3%).

The most common Preferred Terms (PTs) were hypercholesterolaemia (14.4%), osteoarthritis (12.5%), and dyslipidaemia (9.3%). Frequencies of concomitant diseases were comparable across the treatment groups.

In trial 1235.6 the overall frequency (83.0%,) of concomitant diseases was similar to that in trial 1235.5 (82.4%). The most common SOCs (≥20.0% patients overall) in trial 1235.6 were *Metabolism and Nutrition Disorders* (51.5%), *Cardiac Disorders* (25.0%), and *Musculoskeletal and Connective Tissue Disorders* (20.2%). The most common diseases in trial 1235.6 were hyperlipidaemia (17.6%), obesity (13.4%), and hypercholesterolaemia (10.3%). Frequencies of concomitant diseases were comparable across the treatment groups.

Concomitant diseases that were more common in trial 1235.6 than in trial 1235.5 (difference ≥10.0% patients) comprised *Metabolism and Nutrition Disorders* (51.1% vs. 40.7%) and *Cardiac Disorders* (25.0% vs. 10.1%). Hypercholesterolaemia was one of the most common diseases in both trials.

In trial 1235.1the FAS and DBP100 subset were almost identical in their patient characteristics. No item differed by more than 3.0% and the vast majority of items differed by less than 1.0%.

Efficacy Results

Efficacy in trials 1235.5 and 1235.6 – Add on therapy

Primary endpoint: change from baseline in diastolic blood pressure

The change in mean trough sDBP between baseline and last visit was the primary endpoint in trials 1235.5 and 1235.6. Baseline DBP values were comparable across treatment groups within each trial (Table 9). Mean DBP decreased in all treatment groups after 8 weeks of treatment with the double-blind trial medication. Decreases in the groups receiving combination therapy were consistently higher than those in the groups receiving amlodipine monotherapy (A5 and A10 in trial 1235.5, A10 in trial 1235.6). In both trials, the highest reductions of DBP were seen in the combination groups receiving T80.

Table 9: Change in adjusted mean DBP [mmHg] from baseline to end of trials 1235.5 and 1235.6 (FAS)

Characteristic	Trial 1235.5				Trial 1235.6		
	A5	A10	T40/A5	T80/A5	A10	T40/A10	T80/A10
Number of patients, N	255	261	270	271	305	306	310
Baseline, mean (SD)	96.4 (5.3)	96.5 (4.8)	96.9 (5.1)	96.5 (4.9)	95.6 (4.0)	95.5 (4.0)	95.6 (4.1)
End of trial, mean (SD)	90.7 (8.6)	88.6 (8.2)	87.5 (8.5)	85.8 (8.8)	89.5 (6.7)	86.6 (6.8)	86.7 (6.6)
Change from baseline, mean (SD)	−5.7 (7.6)	−7.9 (7.0)	−9.4 (8.0)	−10.6 (7.9)	−6.1 (6.5)	−8.8 (7.0)	−8.9 (6.6)
Adjusted* change from baseline, mean (SE)	−5.7 (0.49)	−8.0 (0.49)	−9.4 (0.48)	−10.6 (0.48)	−6.5 (0.45)	−9.2 (0.45)	−9.3 (0.45)
Adjusted* difference to A5							
Mean (SE)	–	–	−3.6 (0.64)	−4.9 (0.64)	–	–	–
95% CI	–	–	(−4.9, −2.4)	(−6.2, −3.7)	–	–	–
p-value	–	–	<0.0001	<0.0001	–	–	–
Adjusted* difference to A10							
Mean (SE)	–	–	−1.4 (0.64)	−2.7 (0.64)	–	−2.8 (0.52)	−2.8 (0.51)
95% CI	–	–	(−2.7, −0.1)	(−3.9, −1.4)	–	(−3.8, −1.7)	(−3.9, −1.8)
p-value	–	–	0.0288	<0.0001	–	<0.0001	<0.0001

Note: Baseline was the pre-dose BP measurement at the last visit before the first dose of randomised treatment.
* Adjusted for baseline trough seated DBP and country.

Trial 1235.5 showed that T40/A5 and T80/A5 were both superior to A5 and A10 monotherapy in reducing DBP in patients who had not adequately responded to 6 weeks treatment with A5 ($p<0.0001$ for T40/A5 vs A5, T80/A5 vs A5, T80/A5 vs A10; $p=0.0288$ for T40/A5 vs A10). Similarly, trial 1235.6 showed that T80/A10 and T40/A10 were both superior to A10 monotherapy in non-responders to 6 weeks of treatment with A10 ($p<0.0001$).

In both trials there were reductions between baseline and end of trial in all treatment groups although patients had already been pre-treated with amlodipine monotherapy for 6 weeks. At the end of the 8-week randomised period, DBP decreased further by 5.7 mmHg (adjusted means) in the A5 group of trial 1235.5 and by 6.5 mmHg in the A10 group of trial 1235.6. This phenomenon has also been reported in other trials investigating BP lowering therapy in non-responder populations. It may be that the 6-week run-in phase may not have been long enough to establish a stable BP situation and express the complete treatment effect of amlodipine.

Change from baseline in systolic blood pressure

Results are summarised in Table 10. The overall pattern of changes in SBP was similar to that for DBP. Mean SBP decreased in all treatment groups after 8 weeks of treatment with the double-blind trial medication. Decreases in the groups receiving combination therapy were consistently higher than those in the groups receiving amlodipine monotherapy. Within each trial, the highest adjusted decreases were generally seen in the combination group receiving T80.

Table 10: Change in adjusted mean SBP [mmHg] from baseline to end of trials 1235.5 and 1235.6 (FAS)

Characteristic	Trial 1235.5				Trial 1235.6		
	A5	A10	T40/A5	T80/A5	A10	T40/A10	T80/A10
Number of patients, N	255	261	270	271	305	306	310
Baseline, mean (SD)	150.5 (13.4)	149.0 (11.8)	149.7 (12.3)	148.7 (11.7)	146.8 (10.2)	148.1 (9.4)	147.4 (9.4)
End of trial, mean (SD)	144.3 (15.4)	138.4 (12.6)	136.5 (13.6)	134.4 (14.7)	140.2 (11.3)	137.3 (11.3)	136.7 (10.6)
Change from baseline, mean (SD)	−6.2 (12.3)	−10.6 (10.7)	−13.2 (11.8)	−14.4 (12.4)	−6.6 (10.0)	−10.8 (10.6)	−10.7 (10.1)
Adjusted* change from baseline, mean (SE)	−6.2 (0.73)	−11.1 (0.72)	−13.6 (0.71)	−15.0 (0.71)	−7.4 (0.66)	−11.1 (0.66)	−11.3 (0.66)
Adjusted* difference to A5							
Mean (SE)	–	–	−7.4 (0.95)	−8.8 (0.95)	–	–	–
95% CI	–	–	(−9.2, −5.5)	(−10.7,−6.9)	–	–	–
p-value	–	–	<0.0001	<0.0001	–	–	–
Adjusted* difference to A10							
Mean (SE)	–	–	−2.4 (0.95)	−3.9 (0.95)	–	−3.7 (0.76)	−3.9 (0.76)
95% CI	–	–	(−4.3, −0.6)	(−5.7, −2.0)	–	(−5.2, −2.2)	(−5.3, −2.4)
p-value	–	–	0.0100	<0.0001	–	<0.0001	<0.0001

Note: Baseline was the pre-dose BP measurement at the last visit before the first dose of randomised treatment.
* Adjusted for baseline trough seated SBP and country.

Trial 1235.5 showed that T80/A5 and T40/A5 were both superior to A5 and A10 monotherapy in reducing SBP in patients who had not adequately responded to 6 weeks treatment with A5 ($p<0.0001$ for T40/A5 vs A5, T80/A5 vs A5, T80/A5 vs A10; $p=0.0100$ for T40/A5 vs A10). Trial 1235.6 showed that T80/A10 and T40/A10 were both superior to A10 monotherapy in non-responders to 6 weeks of treatment with A10 ($p<0.0001$).

As for DBP, substantial reductions in SBP from baseline were observed in all treatment groups although patients had already been pre-treated with amlodipine monotherapy for 6 weeks. At the end of the 8-week randomised period, SBP decreased further by 6.2 mmHg (adjusted means) in the A5 group of trial 1235.5 and by 7.4 mmHg in the A10 group of trial 1235.6.

Changes in blood pressure over time

Mean DBP and SBP were comparable across treatment groups both at the start of the run-in phase and at baseline after 6 weeks of treatment with amlodipine monotherapy (A5 in trial 1235.5, A10 in trial 1235.6) (see Table 11). The run-in treatment led to comparable decreases in BP values across the treatment groups within each trial. BP values continued to decrease during the double-blind treatment phase, with significantly larger decreases in the combination therapy groups than in the amlodipine monotherapy groups. Most of the antihypertensive effect was already apparent within 4 weeks of treatment.

Table 11: Mean DBP and SBP [mmHg] over time in trials 1235.5 and 1235.6 (FAS)

Characteristic	Trial 1235.5				Trial 1235.6		
	A5	A10	T40/A5	T80/A5	A10	T40/A10	T80/A10
Number of patients, N	255	261	270	271	305	306	310
DBP, mean (SD)							
Start of run-in	101.6 (5.3)	101.4 (5.1)	101.4 (5.3)	101.3 (5.2)	101.3 (4.9)	101.2 (5.0)	101.4 (4.8)
Baseline	96.4 (5.3)	96.5 (4.8)	96.9 (5.1)	96.5 (4.9)	95.6 (4.0)	95.5 (4.0)	95.6 (4.1)
Change: baseline to week 4	−5.1 (7.0)	−7.7 (7.1)	−9.1 (7.6)	−9.9 (7.9)	−5.8 (6.0)	−7.6 (6.9)	−7.7 (6.6)
Change: baseline to week 8*	−5.7 (7.6)	−7.9 (7.0)	−9.4 (8.0)	−10.6 (7.9)	−6.1 (6.5)	−8.8 (7.0)	−8.9 (6.6)
SBP, mean (SD)							
Start of run-in	158.9 (14.0)	158.8 (13.2)	157.0 (13.6)	157.1 (13.6)	158.2 (11.2)	159.8 (12.2)	159.9 (12.5)
Baseline	150.5 (13.4)	149.0 (11.8)	149.7 (12.3)	148.7 (11.7)	146.8 (10.2)	148.1 (9.4)	147.4 (9.4)
Change: baseline to week 4	−4.4 (11.0)	−9.7 (9.8)	−11.3 (11.4)	−12.0 (11.4)	−6.1 (8.3)	−9.5 (9.8)	−8.4 (10.1)
Change: baseline to week 8*	−6.2 (12.3)	−10.6 (10.7)	−13.2 (11.8)	−14.4 (12.4)	−6.6 (10.0)	−10.8 (10.6)	−10.7 (10.1)

Note: Baseline was the pre-dose BP measurement at the last visit before the first dose of randomised treatment.
* Last observation carried forward.

Blood pressure control rates, response rates and categories

The BP lowering effect in trials 1235.5 and 1235.6 was analysed according to pre-defined criteria for DBP control, SBP control, DBP response, SBP response and BP categories (optimal, normal, high-normal, Grade 1–3 hypertension). Results of these analyses are presented in Table 12 and confirm the superiority of the T/A combination therapy over amlodipine monotherapy. The overall proportions of patients achieving DBP and SBP control and response at the end of trials 1235.5 and 1235.6 were higher in the combination therapy groups than in the amlodipine monotherapy groups. All control and response rates in the T80 combination groups were higher than in the T40 combination groups with the exception of DBP control <80 mmHg in trial 1235.6.

In trial 1235.5, the proportions of patients achieving DBP control or DBP response in the T40/A5 and T80/A5 groups were significantly higher than in the A5 group ($p \leq 0.0010$). Similarly, the proportions of patients achieving SBP control or SBP response in the T40/A5 and T80/A5 groups were significantly higher than in the A5 group ($p < 0.0001$). More patients achieved DBP control or a DBP response on T40/A5 or T80/A5 than on A10 but the differences between the treatment groups did not generally reach statistical significance. The SBP control and response rates in the combination therapy groups were also higher than in the A10 group; all of the treatment differences with respect to the A10 group were statistically significant apart from that for SBP control <140 mmHg in the T40/A5 group.

Significantly more patients in the T40/A10 and T80/A10 groups of trial 1235.6 achieved DBP control or DBP response than in the A10 group ($p < 0.005$). Similarly, more patients in the combination groups achieved SBP control (<130, <140 mmHg) or SBP response than in the A10 group; all of the treatment differences with respect to the A10 group were statistically significant apart from that for SBP control <130 mmHg in the T40/A10 group.

Table 12: BP control rates and categories at end of trials 1235.5 and 1235.6 (FAS)

Characteristic	Trial 1235.5				Trial 1235.6		
	A5	A10	T40/A5	T80/A5	A10	T40/A10	T80/A10
Number of patients, N	255	261	270	271	305	306	310
BP control and response rates, N (%) [1]							
DBP <80 mmHg	18 (7.1)	31 (11.9)	44 (16.3)	59 (21.8)	18 (5.9)	39 (12.7)	39 (12.6)
p-value vs A5			0.0009	<0.0001			
p-value vs A10			0.1379	0.0022		0.0044	0.0045
DBP <90 mmHg	107 (42.0)	148 (56.7)	153 (56.7)	173 (63.8)	156 (51.1)	195 (63.7)	206 (66.5)
p-value vs A5			0.0005	<0.0001			
p-value vs A10			0.9923	0.0866		0.0019	0.0001
DBP response	116 (45.5)	163 (62.5)	177 (65.6)	187 (69.0)	163 (53.4)	202 (66.0)	213 (68.7)
p-value vs A5			<0.0001	<0.0001			
p-value vs A10			0.4489	0.1046		0.0018	0.0001
SBP <130 mmHg	35 (13.7)	61 (23.4)	86 (31.9)	104 (38.4)	55 (18.0)	70 (22.9)	79 (25.5)
p-value vs A5			<0.0001	<0.0001			
p-value vs A10			0.0160	<0.0001		0.1413	0.0226
SBP <140 mmHg	100 (39.2)	142 (54.4)	162 (60.0)	178 (65.7)	153 (50.2)	180 (58.8)	187 (60.3)
p-value vs A5			<0.0001	<0.0001			
p-value vs A10			0.1406	0.0054		0.0250	0.0076
SBP response	106 (41.6)	155 (59.4)	175 (64.8)	188 (69.4)	162 (53.1)	188 (61.4)	193 (62.3)
p-value vs A5			<0.0001	<0.0001			
p-value vs A10			0.1551	0.0124		0.0316	0.0160
BP categories, N (%) [2]							
BP optimal	2 (0.8)	5 (1.9)	19 (7.0)	21 (7.7)	0 (0.0)	12 (3.9)	6 (1.9)
BP normal	23 (9.0)	30 (11.5)	35 (13.0)	51 (18.8)	36 (11.8)	43 (14.1)	50 (16.1)
BP high-normal	42 (16.5)	68 (26.1)	63 (23.3)	67 (24.7)	77 (25.2)	91 (29.7)	106 (34.2)
Grade 1 hypertension	118 (46.3)	126 (48.3)	127 (47.0)	110 (40.6)	157 (51.5)	139 (45.4)	133 (42.9)
Grade 2 hypertension	66 (25.9)	32 (12.3)	25 (9.3)	19 (7.0)	34 (11.1)	21 (6.9)	14 (4.5)
Grade 3 hypertension	4 (1.6)	0 (0.0)	1 (0.4)	3 (1.1)	1 (0.3)	0 (0.0)	1 (0.3)
p-value vs A5			<0.0001	<0.0001			
p-value vs A10			0.1091	0.0005		0.0031	<0.0001

DBP response: seated DBP <90 mmHg or reduction from baseline ≥10 mmHg
SBP response: seated SBP <140 mmHg or reduction from baseline ≥20 mmHg
(Note: In trial reports, definition of SBP response used reduction from baseline ≥15 mmHg.)
BP optimal: SBP <120 mmHg and DBP <80 mmHg; BP normal: SBP <130 mmHg and DBP <85 mmHg but not 'optimal'
BP high-normal: SBP <140 mmHg and DBP <90 mmHg but not 'normal'
Grade 1 hypertension: SBP <160 mmHg and DBP <100 mmHg but not 'high-normal'
Grade 2 hypertension: SBP <180 mmHg and DBP <110 mmHg but not 'Grade 1 hypertension'
Grade 3 hypertension: SBP ≥180 mmHg or DBP ≥110 mmHg

[1] p-Values calculated by logistic regression adjusting for country.
[2] p-Values calculated by van Elteren test.

Blood pressure categories

At baseline 99.9% (1056/1057) of the patients in trial 1235.5 and 99.2% (914/921) of the patients in trial 1235.6 had Grade 1 to Grade 3 hypertension. At the end of the trials the proportions of patients with these categories had decreased considerably in all treatment groups with corresponding increases in the proportions of patients in the optimal, normal and high normal categories to 40.3% (426/1057) in trial 1235.5 and 45.7% (421/921) in trial 1235.6 (see Table 12). The frequencies of patients with optimal, normal, and high-normal BP were higher in the combination therapy groups than in the amlodipine monotherapy groups in both trials: trial 1235.5: A5 26.3%, A10 39.5%, T40/A5 43.3%, T80/A5 51.3%; trial 1235.6: A10 37.0%, T40/A10 47.7%, T80/A10 52.3%. Frequencies of Grade 3 hypertension were low in all treatment groups (≤1.6%). Comparison of BP categories in trial 1235.5 showed that the T40/A5 and T80/A5 groups were both statistically superior to the A5 monotherapy group ($p < 0.0001$) and that the T80/A5 group was superior to the A10 group ($p = 0.0005$). In trial

1235.6, the T40/A10 and T80/A10 groups were both statistically superior to the A10 group (p = 0.0031 and <0.0001, respectively).

Probability of achieving blood pressure control depending on baseline BP

The results of the probability of achieving DBP control using the criteria of <90 mmHg and <80 mmHg are presented in Table 13. The combination therapies had a higher probability of achieving DBP control than the amlodipine monotherapies. Odds ratios were all in favour of the combination therapy groups with statistically significant benefits for T40/A5 and T80/A5 vs A5 in trial 1235.5 (p<0.0001) and for T40/A10 and T80/A10 vs A10 in trial 1235.6 (p ≤0.0018). In addition, the T40/A5 and T80/A5 combination groups were superior to A10 for the more stringent goal of <80 mmHg.

Table 13: Probability of achieving DBP control (<90, <80 mmHg) at end of trials 1235.5 and 1235.6 adjusted for baseline DBP (FAS)

Characteristic	Trial 1235.5				Trial 1235.6		
	A5	A10	T40/A5	T80/A5	A10	T40/A10	T80/A10
Number of patients, N	255	261	270	271	305	306	310
Probability DBP <90 mmHg	**0.39**	**0.56**	**0.59**	**0.65**	**0.51**	**0.64**	**0.67**
95% CI	(0.32, 0.46)	(0.50, 0.63)	(0.52, 0.65)	(0.58, 0.70)	(0.45, 0.57)	(0.58, 0.69)	(0.62, 0.72)
Comparison vs A5							
Odds ratio	–	–	2.22	2.86	–	–	–
95% CI	–	–	(1.50, 3.27)	(1.93, 4.22)	–	–	–
p-value	–	–	<0.0001	<0.0001	–	–	–
Comparison vs A10							
Odds ratio	–	–	1.09	1.41	–	1.70	1.95
95% CI	–	–	(0.74, 1.60)	(0.95, 2.07)	–	(1.22, 2.36)	(1.40, 2.73)
p-value	–	–	0.6637	0.0865	–	0.0018	<0.0001
Probability DBP <80 mmHg	**0.05**	**0.10**	**0.16**	**0.18**	**0.05**	**0.12**	**0.12**
95% CI	(0.03, 0.09)	(0.06, 0.15)	(0.12, 0.21)	(0.13, 0.24)	(0.03, 0.08)	(0.09, 0.16)	(0.08, 0.16)
Comparison vs A5							
Odds ratio	–	–	3.59	3.99	–	–	–
95% CI	–	–	(1.73, 7.44)	(1.90, 8.42)	–	–	–
p-value	–	–	0.0006	0.0003	–	–	–
Comparison vs A10							
Odds ratio	–	–	1.77	1.97	–	2.73	2.69
95% CI	–	–	(1.01, 3.11)	(1.10, 3.54)	–	(1.38, 5.40)	(1.36, 5.33)
p-value	–	–	0.0469	0.0229	–	0.0040	0.0045

The combination therapies also had a higher probability of achieving SBP control <140 mmHg and <130 mmHg than the amlodipine monotherapies. Odds ratios were all in favour of the combination therapies with statistically significant benefits for T40/A5 and T80/A5 vs A5 in trial 1235.5 (p<0.0001) as well as for T40/A10 and T80/A10 vs A10 in trial 1235.6 (p ≤0.0016). With one exception (T40/A5 for SBP control <140 mmHg), the T40/A5 and T80/A5 combinations were statistically superior to A10 monotherapy.

Table 14 shows the probability of achieving BP control at the end of trial adjusted for baseline DBP using criteria of <140/90 mmHg and <130/80 mmHg.. The probability of achieving BP control with the combination therapies was consistently higher than with the amlodipine monotherapies, supporting the clinical benefit of the addition of telmisartan to amlodipine. The odds ratios were statistically significantly in favour of the combination therapies with the exception of T40/A5 vs A10 (BP control <140/90 mmHg) and T80/A5 vs A10 (BP control <130/90 mmHg) in trial 1235.5.

Table 14: Probability of achieving optimal BP control at end of trials 1235.5 and 1235.6 adjusted for baseline DBP (FAS)

Characteristic	Trial 1235.5				Trial 1235.6		
	A5	A10	T40/A5	T80/A5	A10	T40/A10	T80/A10
Number of patients, N	255	261	270	271	305	306	310
Probability BP control (<140/90 mmHg)	**0.23**	**0.36**	**0.43**	**0.50**	**0.36**	**0.47**	**0.52**
95% CI	(0.18, 0.30)	(0.30, 0.43)	(0.37, 0.49)	(0.44, 0.57)	(0.31, 0.42)	(0.42, 0.53)	(0.47, 0.58)
Comparison vs A5							
Odds ratio	–	–	2.46	3.33	–	–	–
95% CI	–	–	(1.63, 3.72)	(2.22, 5.01)	–	–	–
p-value	–	–	<0.0001	<0.0001	–	–	–
Comparison vs A10							
Odds ratio	–	–	1.33	1.80	–	1.60	1.94
95% CI	–	–	(0.90, 1.96)	(1.23, 2.64)	–	(1.14, 2.23)	(1.39, 2.70)
p-value	–	–	0.1475	0.0025	–	0.0059	<0.0001
Probability BP control (<130/80 mmHg)	**0.02**	**0.04**	**0.12**	**0.09**	**0.03**	**0.08**	**0.09**
95% CI	(0.01, 0.05)	(0.02, 0.08)	(0.08, 0.16)	(0.06, 0.14)	(0.01, 0.06)	(0.05, 0.12)	(0.06, 0.12)
Comparison vs A5							
Odds ratio	–	–	5.69	4.44	–	–	–
95% CI	–	–	(2.13, 15.2)	(1.57, 12.5)	–	–	–
p-value	–	–	0.0005	0.0048	–	–	–
Comparison vs A10							
Odds ratio	–	–	2.81	2.19	–	3.21	3.48
95% CI	–	–	(1.30, 6.07)	(0.95, 5.05)	–	(1.30, 7.89)	(1.43, 8.51)
p-value	–	–	0.0085	0.0658	–	0.0113	0.0062

Incidence of oedema

Oedema is a known dose dependent side effect of amlodipine and the incidence of oedema was a co-primary endpoint in trial 1235.5 and a secondary endpoint in trial 1235.6. For the analysis of this endpoint, the 3 MedDRA PTs peripheral oedema, generalised oedema, and oedema were selected and combined into the category 'general oedema'.[10] In the pooled T/A group of trial 1235.5, 4.4% of patients experienced oedema (T40/A5: 5.2%, T80/A5: 3.7%), while in the A10 group the incidence was significantly higher (24.9%). Patients treated with T40/A5 or T80/A5 combinations were significantly less likely to experience new or worsening cases of the category 'general oedema' than patients treated with A10. The rate of 'general oedema' was lower in the T40/A5 and T80/A5 groups than that in the A5 group (8.2%). This is a favourable result. It is thought that the CCB-induced dilation of pre-capillary vessels that causes oedema is partly counterbalanced by the ARB-induced post-capillary dilation of vessels. The co-administration of an ARB could thus mitigate the occurrence of oedema caused by a CCB.

The rate of peripheral oedema during the 6-week A5 run-in treatment was 6.1% and was 8.2% for continued treatment with A5 during the randomised phase. Thus, A5 treatment continued to result in new and/or worsening cases of peripheral oedema after randomisation. The occurrence of oedema is thus not restricted to the first days or weeks of treatment with A5 but remains an issue during longer treatment. In the A10 group a higher incidence of oedema 24.9% was observed during the randomised phase and can be explained by the increase in the amlodipine dose from 5 to 10 mg/day.

[10] MedDRA = Medical Dictionary for Regulatory Activities.

In the pooled T/A group, 4.3% of patients experienced new or worsening events included in the pre-defined category 'general oedema' (T40/A5: 5.1%, T80/A5: 3.6%), while in the A10 group, the incidence was substantially higher with 27.2%.

In contrast to trial 1235.5, similar oedema rates were reported for the pooled T/A group (7.3%; T40/A10: 6.2%, T80/A10: 8.4%) and the A10 group (6.6%) in trial 1235.6. During run in treatment with A5 and A10 peripheral oedema was the most frequently reported AE (A5: 3.1%, A10: 16.6%) and led to discontinuation in about one-third of these patients. Thus, a substantial number of patients who did not tolerate amlodipine monotherapy treatment did not continue during the run in phase and only patients who tolerated amlodipine monotherapy were randomised. The lower incidence of peripheral oedema during A10 treatment in the randomised phase (about 7% in each treatment group) may be accounted for by the fact that AEs were only counted if they worsened or occurred for the first time during this phase. It is likely that the pre-treatment of patients with amlodipine for 8 weeks (A5 for 2 weeks followed by A10 for 6 weeks) as well as the inclusion of only patients who did not respond to antihypertensive A10 monotherapy had an influence on the oedema rate observed during the randomised phase.

Subgroup analyses – trials 1235.5 and 1235.6

Age

The majority of patients in both trials were <65 years: 83.1% (878/1057) patients in trial 1235.5 and 78.4% (722/921) patients in trial 1235.6. Reductions of BP were generally greater in the combination treatment groups than in the amlodipine monotherapy groups for each age category. However, in elderly patients in trial 1235.5, similar decreases were seen for DBP in the A10, T40/A5, and T80/A5 groups and for SBP in the A10 and T40/A5 groups. It should be noted that there were fewer patients 65 years of age or older in all treatment groups than patients younger than 65 years. In trial 1235.5, mean decreases in DBP and SBP were slightly greater in elderly patients than in younger patients in the amlodipine monotherapy groups; changes in the combination therapy groups were similar in both age categories. In trial 1235.6, mean decreases in DBP and SBP were slightly greater in elderly patients in all treatment groups.

Gender, BMI

Reductions of BP were greater in the combination treatment groups than in the amlodipine monotherapy groups in both men and women. Mean changes in DBP and SBP were only slightly higher in women than in men in both trials.

Results were analysed for patients with BMI ≥30 kg/m² and with BMI <30 kg/m². Reductions of BP were greater in the combination treatment groups than in the amlodipine monotherapy groups in both BMI categories. There was no consistent pattern of differences in BP reductions in patients with BMI < or ≥30 kg/m², and no changes were clinically relevant.

Evaluator Comment

Trials 1235.5 and 1235.6 were appropriately designed to evaluate the T/A combination therapies used as second-line therapy. The trials can be considered pivotal. In trials 1235.5 and 1235.6, administration of the T/A FDCs for 8 weeks to patients who had not responded to amlodipine (DBP >90 mmHg) resulted in statistically and clinically significantly higher reductions in mean DBP and SBP than amlodipine alone. The benefits of the combination therapy over amlodipine were apparent within 4 weeks of treatment. The superiority of the TA/FDC over amlodipine in this setting was supported by results for other efficacy variables (BP control rates, BP response rates, and probabilities of achieving BP control). For all

endpoints the T80/A5 and T40/A5 groups showed consistently better efficacy than the A5 group; the same was true for the T80/A10 and T40/A10 groups compared to the A10 group. Efficacy results for the T40/A5 and T80/A4 FDCs were accompanied by significantly lower oedema rates compared to full-dose amlodipine monotherapy.

In relation to dose response, Study 1235.5 analyses of efficacy showed that the intake of an increased dose of telmisartan, that is 80 mg rather than 40 mg in combination with A5 tended to results in a greater BP reduction. The increase of the amlodipine dose from A5 to A10 also brought about larger BP reductions. However, the incidence of oedema adverse events substantially increased upon intake of A10.

In Study 1235.6 analyses of efficacy showed that the intake of an increased dose of telmisartan, that is 80 mg rather than 40 mg, in combination with A10 showed only a small trend to a greater BP reduction.

Overall, the evaluator considered that the data were sufficient to support that the combination T/A FDCs are effective when used as add on therapy for the treatment of hypertension.

Trial 1235.1- Initial therapy

Primary endpoint: change from baseline in diastolic blood pressure

FAS

Each combination therapy produced greater mean changes from baseline in trough sDBP than the respective monotherapies. At the end of trial 1235.1, mean DBP changes ranged from –16.0 to –19.6 mmHg for the key combination treatment groups and from –13.0 to –16.5 mmHg for the monotherapy groups. The greatest change (–19.6 mmHg) was observed in the telmisartan and concomitant high-dose amlodipine (T40+A10 and T80+A10) treatment groups. The change observed in the A10 monotherapy group was generally comparable to the changes in the key combination treatment groups containing A5. The mean change from baseline in trough sDBP was –5.9 mmHg in the placebo group. Results are summarised in Table 15.

Table 15: Observed mean DBP [mmHg] at baseline, end-of-trial*, and change from baseline in key combination treatment groups and respective monotherapies, including placebo, in trial 1235.1 (FAS)

		A0	A5	A10
Number of patients, N	T0	46	137	124
Baseline, Mean (SD)		102.5 (4.8)	102.4 (4.5)	101.2 (4.0)
End of trial, Mean (SD)		96.6 (11.3)	89.3 (9.3)	84.7 (8.0)
Change from baseline, Mean (SD)		-5.9 (9.4)	-13.0 (7.9)	-16.5 (7.1)
Number of patients, N	T40	129	141	123
Baseline, Mean (SD)		102.2 (4.7)	101.6 (4.1)	101.6 (3.8)
End of trial, Mean (SD)		89.1 (10.3)	85.7 (7.7)	82.0 (8.3)
Change from baseline, Mean (SD)		-13.1 (10.1)	-16.0 (7.6)	-19.6 (7.9)
Number of patients, N	T80	132	143	136
Baseline, Mean (SD)		101.5 (4.5)	101.8 (4.5)	101.3 (3.9)
End of trial, Mean (SD)		87.9 (9.3)	84.0 (8.8)	81.7 (7.9)
Change from baseline, Mean (SD)		-13.6 (8.7)	-17.8 (8.5)	-19.6 (7.9)

Note: Baseline was the pre-dose BP measurement at the last visit before the first dose of randomised treatment.
* Missing values replaced by LOCF.

The effects of each of the four key combination treatments involving telmisartan 40 or 80 mg and amlodipine 5 or 10 mg on the changes from baseline in trough sDBP were compared to

the effects of the respective individual monotherapies using the full ANCOVA that included all 16 treatment groups for the FAS (Table 16). Each of the four key combination treatments reduced trough sDBP to a significantly greater degree than each of the respective individual monotherapies.

Table 16: Adjusted* mean DBP change from baseline [mmHg] in key combination treatment groups and respective monotherapies, including placebo, in trial 1235.1 (FAS)

		A0	A5	A10
Number of patients, N	T0	46	137	124
End of trial, Mean (SE)		-6.2 (1.19)	-13.4 (0.69)	-17.1 (0.73)
Number of patients, N	T40	129	141	123
End of trial, Mean (SE)		-13.4 (0.71)	-16.5 (0.68)	-20.2 (0.73)
Difference to A component, Mean (SE)			-3.1 (0.97)	-3.1 (1.02)
95% CI			(-5.0, -1.2)	(-5.1, -1.1)
p-value			0.0013	0.0023
Difference to T component, Mean (SE)			-3.1 (0.98)	-6.8 (1.01)
95% CI			(-5.0, -1.2)	(-8.8, -4.8)
p-value			0.0016	<0.0001
Number of patients, N	T80	132	143	136
End of trial, Mean (SE)		-14.0 (0.71)	-18.2 (0.68)	-20.1 (0.70)
Difference to A component, Mean (SE)			-4.9 (0.96)	-3.0 (1.00)
95% CI			(-6.7, -3.0)	(-5.0, -1.1)
p-value			<0.0001	0.0024
Difference to T component, Mean (SE)			-4.2 (0.97)	-6.1 (0.98)
95% CI			(-6.1, -2.3)	(-8.0, -4.1)
p-value			<0.0001	<0.0001

Note: Baseline was the pre-dose BP measurement at the last visit before the first dose of randomised treatment.
* Adjusted for baseline and country effect.

DBP100

Results of the analyses of the DBP data for the DBP100 subset were very similar to those observed in the FAS. In the four key combination treatment groups and the respective monotherapies, increasing dose-related DBP reductions were observed, with the greatest reduction in the T80+A10 treatment group. Across the four key combination treatment groups, mean trough sDBP changes ranged from –16.8 to –20.4 mmHg and, across the 4 monotherapies, from –13.1 to –17.1 mmHg. Changes in the A10 monotherapy group were comparable to the observed changes in the key combination treatment groups containing A5.

Results for changes from baseline in trough sDBP were compared to the effects of the respective individual monotherapies using the full ANCOVA that included all 16 treatment groups for the DBP100 subset. Similar to the results for the analyses using the FAS, each of the 4 key combination treatments reduced trough sDBP to a significantly greater amount than each of the respective individual monotherapies.

Grade 2/3 subset

Data for the Grade 2/3 subset were consistent with those presented for the FAS and for the DBP100 subset.

Predicted change from baseline in diastolic blood pressure

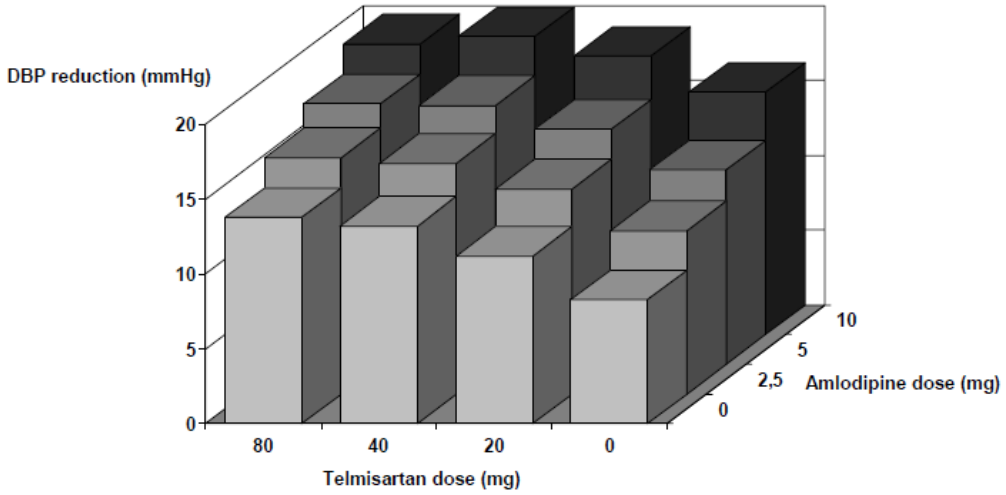
FAS

The predicted mean change from baseline in the trough sDBP according to a response-surface model for the FAS is shown in Table 17 and graphically in Figure 1. This graph shows dose-related changes in DBP with increasing doses of each monotherapy and greater changes with combination therapy. Generally, there are increasing BP reductions with increasing doses of both telmisartan and/or amlodipine with only 1 exception (T40+A10) in the 16-group table.

Table 17: Predicted mean DBP change from baseline [mmHg] according to a Response-surface model in combination treatment groups and respective monotherapies in trial 1235.1 (FAS)

	A0	A2.5	A5	A10
T0	-8.3	-10.9	-13.0	-16.2
T20	-11.2	-13.7	-15.7	-18.6
T40	-13.2	-15.4	-17.3	-19.9
T80	-13.8	-15.8	-17.4	-19.4

Figure 1: Predicted mean DBP change from baseline [mmHg] according to a response-surface model in trial 1235.1 (FAS)



Change and predicted change from baseline in systolic blood pressure

FAS

The key combination treatment groups produced greater mean reductions from baseline SBP than the respective monotherapies, indicating an additive effect. Increasing doses of each monocomponent produced incremental SBP changes from baseline with the exception of the T80+A0 treatment group, where the change in SBP was similar to that seen for the T40+A0 treatment group. The greatest effect on SBP (–25.8 mmHg change) was observed in the T80+A10 treatment group. At the end of the trial, mean SBP changes ranged from –13.2 to –19.8 mmHg for the monotherapies and from –21.0 to –25.8 mmHg for the key combination therapies. Baseline mean SBP readings were within 1.5 mmHg across the key combination and respective monotherapy groups, with values ranging from 152.1 to 153.6 mmHg.

The effects of treatment with each of the four key combination treatments involving telmisartan 40 or 80 mg and amlodipine 5 or 10 mg on the change from baseline for trough sSBP were compared to the effects of the respective individual monotherapies and results are presented in Table 18. As with the DBP results for the FAS, these data show that each of the 4 key combination treatments reduced trough sSBP to a significantly greater degree than the respective individual monotherapies.

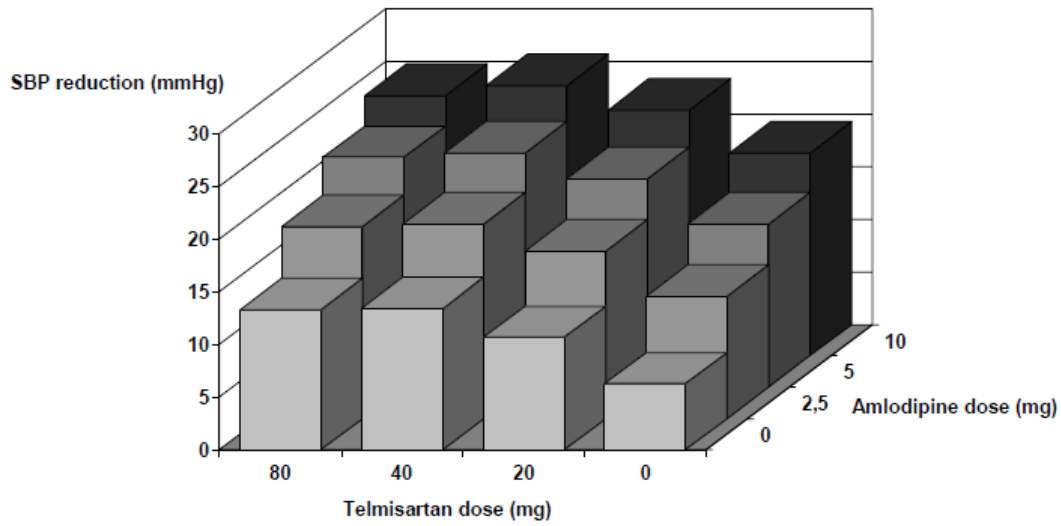
Table 18: Adjusted* mean SBP change from baseline [mmHg] in key combination treatment groups and respective monotherapies, including placebo, in trial 1235.1 (FAS)

		A0	A5	A10
Number of patients, N	T0	46	137	124
End of trial, Mean (SE)		-2.5 (1.82)	-15.4 (1.06)	-20.7 (1.11)
Number of patients, N	T40	129	141	123
End of trial, Mean (SE)		-14.6 (1.09)	-21.8 (1.05)	-24.7 (1.12)
Difference to A component, Mean (SE)			-6.4 (1.48)	-4.0 (1.57)
95% CI			(-9.3, -3.5)	(-7.1, -0.9)
p-value			<0.0001	0.0108
Difference to T component, Mean (SE)			-7.2 (1.50)	-10.1 (1.55)
95% CI			(-10, -4.3)	(-13, -7.1)
p-value			<0.0001	<0.0001
Number of patients, N	T80	132	143	136
End of trial, Mean (SE)		-14.3 (1.08)	-22.1 (1.04)	-26.4 (1.07)
Difference to A component, Mean (SE)			-6.7 (1.47)	-5.7 (1.53)
95% CI			(-9.6, -3.8)	(-8.7, -2.7)
p-value			<0.0001	0.0002
Difference to T component, Mean (SE)			-7.8 (1.49)	-12.1 (1.51)
95% CI			(-11, -4.9)	(-15, -9.2)
p-value			<0.0001	<0.0001

Note: Baseline was the pre-dose BP measurement at the last visit before the first dose of randomised treatment.
* Adjusted for baseline and country effect.

Predicted response data for the SBP show that increasing doses of combination therapy are associated with greater reductions in SBP (Figure 2). Results are similar to those reported for the predicted change from baseline for the DBP assessment.

Figure 2: Predicted mean SBP change from baseline [mmHg] according to a response-surface model in trial 1235.1 (FAS)



DBP100

Similar to the analyses of the FAS, the greatest reduction in SBP for the DBP100 subset was observed in the T80+A10 treatment group (–25.5 mmHg) and each combination treatment produced greater SBP reductions than observed in the respective monotherapy groups. Across the 4 monotherapies, mean SBP changes ranged from –14.7 to –20.9 mmHg whereas, across the 4 combination therapies, mean SBP changes ranged from –21.7 to –25.5 mmHg. In the placebo treatment group, the mean DBP change was –1.0 mmHg. Reductions in the A10

monotherapy group were generally comparable to the observed changes in the key combination treatment groups containing A5. There were increasing BP reductions with increasing doses of all therapies.

Grade 2/3 subset

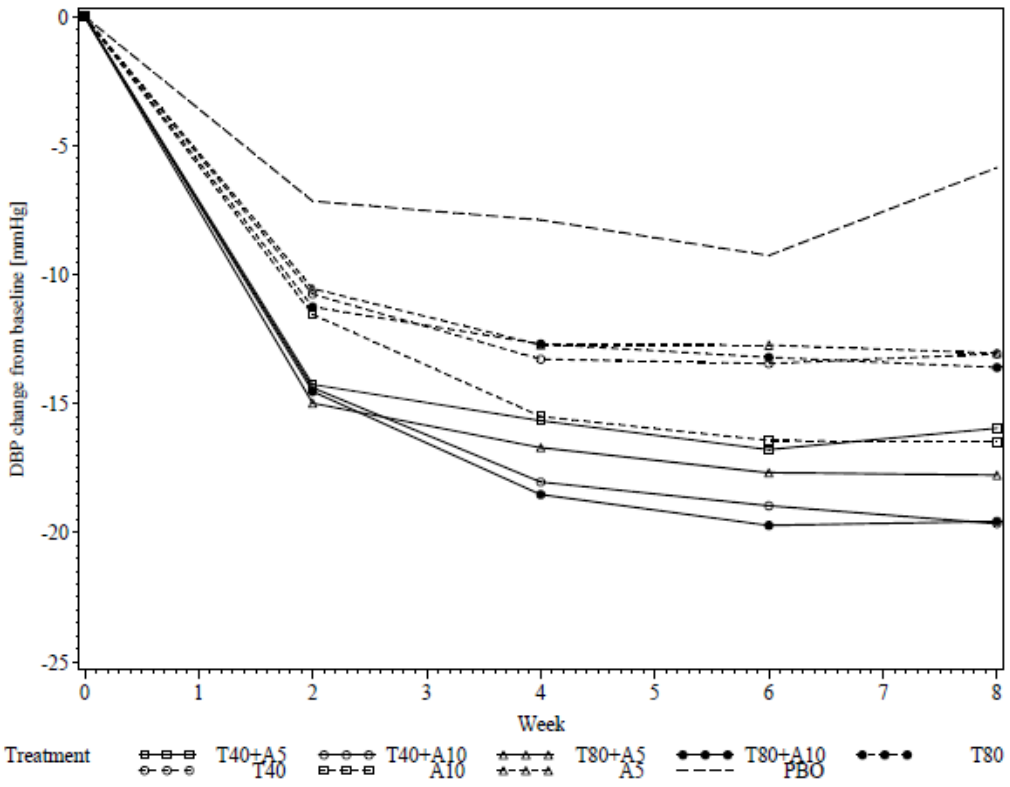
Efficacy data for the Grade 2/3 subset were generally consistent with those presented for the FAS and for the DBP100 subset, with combined therapy being associated with larger reductions in SBP than with respective monotherapies. Across the 3 data sets, SBP reductions ranged from 21 to 27 mmHg for the key combination treatments, 13 to 22 mmHg for the respective monotherapies, and 0 to 2 mmHg for the placebo groups.

Changes in blood pressure over time

FAS

The mean DBP changes from baseline over time for the key combination treatment groups for the FAS are presented graphically in Figure 3. From this graph it can be seen that the majority of the antihypertensive effect is already attained within 2 weeks and was near the maximum observed effect after 4 weeks of therapy. The key combination treatment groups showed larger DBP reductions at earlier time points compared to the monotherapy groups and the placebo group.

Figure 3: Mean DBP change from baseline [mmHg] over time in key combination treatment groups of trial 1235.1

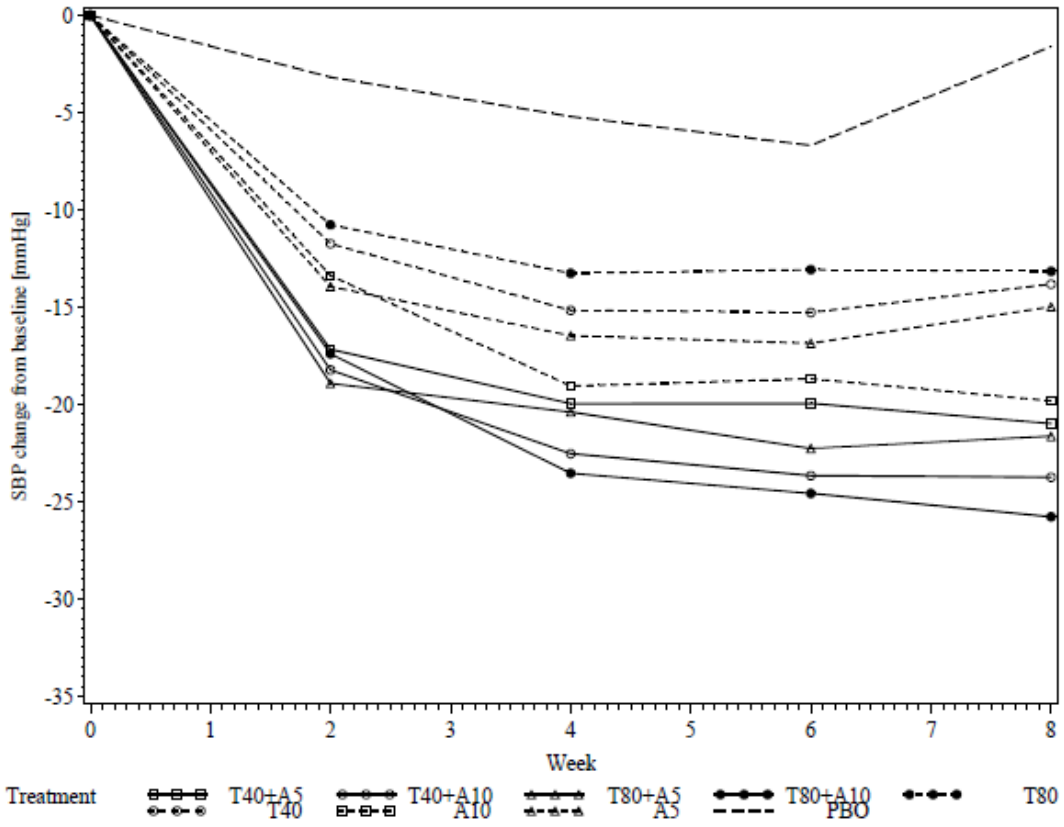


Analyses of adjusted mean DBP changes between baseline and Weeks 2, 4, 6, and 8 were also performed. As patients randomised to treatment with A10 received A5 for the first 2 weeks of therapy, the A10 monotherapy or combination treatment groups were pooled with corresponding A5 monotherapy or combination treatment groups for the analyses at Week 2 so that these analyses reflect the actual received medication doses, that is, A5 was pooled with A10, T40+A5 with T40+A10, and T80+A5 with T80+A10. Mean adjusted DBP

changes at Week 2 in these pooled key combination groups were –14.9 mmHg for T40+A5 and –15.4 mmHg for T80+A5). These changes were substantially higher than those in the corresponding monotherapy groups (T40 –11.2 mmHg, T80 –12.0 mmHg, A5 –11.5 mmHg). All of these treatment differences at Week 2 were statistically significant ($p<0.0001$) confirming that administration of the key combination treatments led to earlier reduction of DBP than the monotherapies. Analyses of adjusted mean changes at the 3 later time points (Weeks 4, 6, and 8) showed that reductions of DBP in the 4 key combination treatment groups were consistently and significantly higher than in the corresponding monotherapy groups ($p \leq 0.028$).

Consistent with the DBP results, mean SBP change from baseline was more rapid for the 4 key combination treatment groups (Figure 4). Results of analyses of mean adjusted SBP changes between baseline and Weeks 2, 4, 6, and 8 were also consistent with those for DBP.

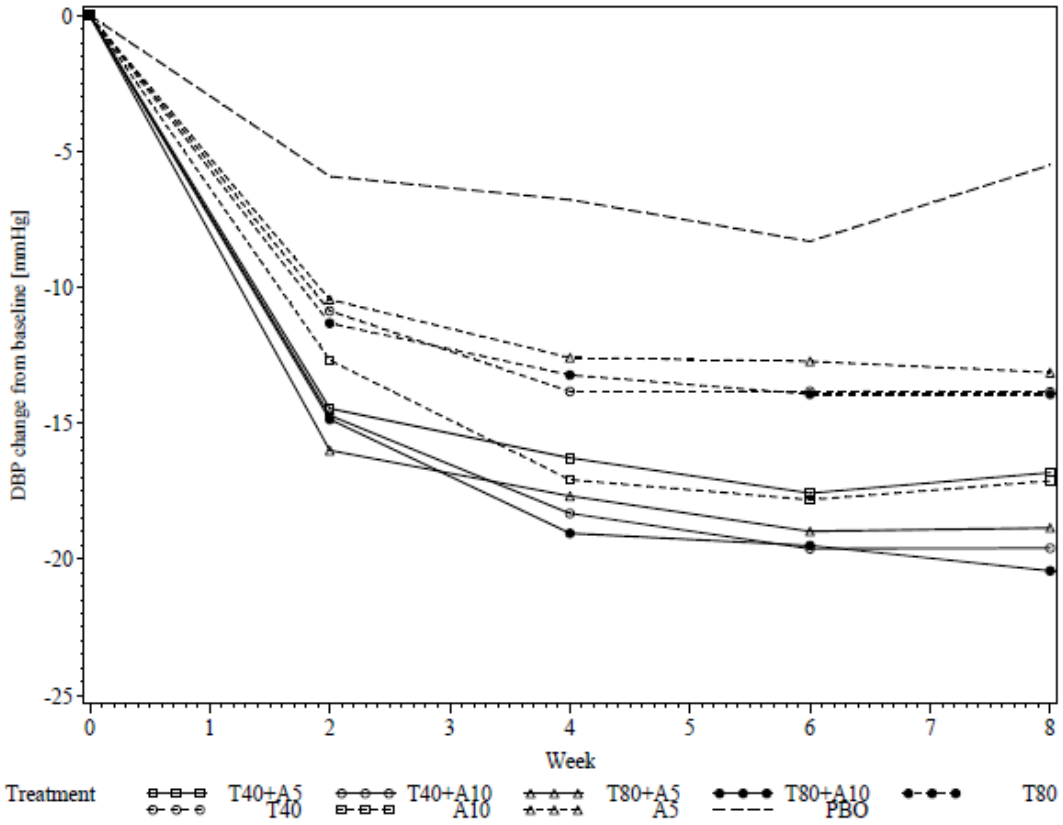
Figure 4: Mean SBP change from baseline [mmHg] over time in key combination treatment groups of trial 1235.1 (FAS)



DBP100

The mean DBP changes from baseline over time for each of the 4 key combination treatment groups for the DBP100 subset are represented graphically in Figure 5. Consistent with the results observed for analyses of the FAS, the majority of the antihypertensive effect was already attained within 2 weeks, approaching the maximum observed antihypertensive effect after 4 weeks of therapy with any of the 4 key combination treatment groups. The mean reductions in DBP from baseline were more rapid for the 4 key combination treatment groups than for the monotherapy groups and the placebo group.

Figure 5: Mean DBP change from baseline [mmHg] over time (DBP100)



Analyses of adjusted mean DBP changes at Weeks 2, 4, 6, and 8 showed similar results to those for the FAS. Mean adjusted DBP changes at Week 2 (with pooling of A5 and corresponding A10 monotherapy and key combination groups) were –15.0 mmHg for T40+A5 and –15.8 mmHg for T80+A5. These changes were substantially higher than those in the corresponding monotherapy groups (T40 –11.2 mmHg, T80 –11.9 mmHg, A5 –11.9 mmHg). All of these treatment differences at Week 2 were highly statistically significant ($p \leq 0.0001$) confirming that administration of the key combination treatments led to earlier reduction of DBP in the DBP100 subset. At the 3 later time points (Weeks 4, 6, and 8), reductions of DBP in the 4 key combination treatment groups were consistently and notably higher than in the corresponding monotherapy groups. Consistent with the DBP results, the mean SBP change from baseline for the DBP100 subset was more rapid for the 4 key combination treatment groups.

The earlier onset of action of the key combination therapies was supported by analyses of time to DBP control (<90 mmHg). The median time to DBP control was considerably shorter with combination therapy (range 15 to 19 days) than with telmisartan or amlodipine monotherapy (range 28 to 42 days). The median times to control in the amlodipine low-dose combination groups T40+A5 and T80+A5 (19 and 16 days) were about30% and 40% shorter, respectively than those in the full-dose monotherapy groups T80 andA10 (28 days).

Grade 2/3 subset

For the patients of the Grade 2/3 hypertension subset, the profile of the change from baseline for trough sDBP and SBP over time was similar to those described above.

Blood pressure control and response rates

FAS

In general, combination therapy was associated with higher rates of BP control and response than observed with the respective monotherapies. Response and control rates for the A10 monotherapy group were similar to the rates for combination therapies that included amlodipine 5 mg while the combination therapies utilising amlodipine 10 mg resulted in the largest responses and control rates (see Table 19). These results are consistent with the results seen for the primary and secondary analyses of BP reduction where the greatest benefit occurs with combination therapy.

Table 19: BP control and response rates in key combination treatment groups and respective monotherapies, including placebo, at the end of trial 1235.1* (FAS)

		A0	A5	A10
		N (%)	N (%)	N (%)
Number of patients	T0	46 (100.0)	137 (100.0)	124 (100.0)
DBP control		14 (30.4)	72 (52.6)	91 (73.4)
DBP response		18 (39.1)	93 (67.9)	106 (85.5)
SBP control		13 (28.3)	77 (56.2)	95 (76.6)
SBP response		14 (30.4)	91 (66.4)	101 (81.5)
Number of patients	T40	129 (100.0)	141 (100.0)	123 (100.0)
DBP control		69 (53.5)	101 (71.6)	101 (82.1)
DBP response		90 (69.8)	114 (80.9)	113 (91.9)
SBP control		72 (55.8)	103 (73.0)	107 (87.0)
SBP response		79 (61.2)	116 (82.3)	111 (90.2)
Number of patients	T80	132 (100.0)	143 (100.0)	136 (100.0)
DBP control		80 (60.6)	107 (74.8)	116 (85.3)
DBP response		103 (78.0)	127 (88.8)	124 (91.2)
SBP control		77 (58.3)	106 (74.1)	112 (82.4)
SBP response		83 (62.9)	116 (81.1)	120 (88.2)

DBP control is defined as seated DBP <90 mmHg.
DBP response is defined as seated DBP <90 mmHg or reduction from baseline ≥10 mmHg.
SBP control is defined as seated SBP <140 mmHg.
SBP response is defined as seated SBP<140 mmHg or reduction from baseline ≥20 mmHg.
(Note: In trial reports, definition of SBP response used reduction from baseline ≥15 mmHg.)
* Missing values replaced by LOCF.

DBP100

For each of the BP response and control variables, results for the DBP100 subset were comparable to those observed for the FAS; the 4 key combination treatments resulted in higher response and control rates than the respective monotherapies. DBP control rates ranged from 69% to 85% in the key combination treatment groups and from 43% to 65% across the respective monotherapy treatment groups. SBP control rates in the key treatment combination groups (range: 67% to 85%) were also notably higher compared to the respective monotherapies (49% to 70%). Table 20 presents the BP response rates by key combination treatment groups and respective monotherapies, including placebo, for the DBP100 subset.

Table 20: BP control and response rates in key combination treatment groups and respective monotherapies, including placebo, at the end of trial 1235.1* (DBP100)

		A0	A5	A10
		N (%)	N (%)	N (%)
Number of patients	T0	35 (100.0)	101 (100.0)	83 (100.0)
DBP control		9 (25.7)	43 (42.6)	54 (65.1)
DBP response		13 (37.1)	64 (63.4)	69 (83.1)
SBP control		7 (20.0)	49 (48.5)	58 (69.9)
SBP response		8 (22.9)	63 (62.4)	63 (75.9)
Number of patients	T40	100 (100.0)	108 (100.0)	96 (100.0)
DBP control		48 (48.0)	75 (69.4)	74 (77.1)
DBP response		69 (69.0)	88 (81.5)	86 (89.6)
SBP control		56 (56.0)	72 (66.7)	82 (85.4)
SBP response		60 (60.0)	83 (76.9)	86 (89.6)
Number of patients	T80	89 (100.0)	106 (100.0)	100 (100.0)
DBP control		44 (49.4)	73 (68.9)	84 (84.0)
DBP response		67 (75.3)	93 (87.7)	93 (93.0)
SBP control		53 (59.6)	72 (67.9)	84 (84.0)
SBP response		59 (66.3)	81 (76.4)	89 (89.0)

DBP control is defined as seated DBP <90 mmHg.
DBP response is defined as seated DBP <90 mmHg or reduction from baseline ≥10 mmHg.
SBP control is defined as seated SBP <140 mmHg.
SBP response is defined as seated SBP<140 mmHg or reduction from baseline ≥20 mmHg.
(Note: In trial report, definition of SBP response used reduction from baseline ≥15 mmHg.)
* Missing values replaced by LOCF.

Grade 2/3 subset

In line with the FAS and with the DBP100 subset, response and control rates with combination therapy were consistently higher than with the respective monotherapies for the Grade 2/3 subset.

Hypertension class

FAS

According to the inclusion and exclusion criteria in trial 1235.1, only patients with uncontrolled hypertension were randomised. After 8 weeks of treatment, the majority of patients in the key combination treatment groups were classified as controlled with their BP by the end of the trial. The proportions of patients with optimal, normal, or high normal BP in the 4 key combination treatment groups ranged from 59% (T40+A5) to 76% (T80+A10) and were thus considerably higher than in the placebo group (20%) and in the monotherapy groups where 42% (T80+A0) to 64% (T0+A10) of the patients were controlled at the end of the trial.

In the combination treatment groups, the proportions of Grade 2/3 hypertensives were considerably lower, ranging from 2% to 7%. For patients receiving the respective monotherapies, the proportions of Grade 2/3 hypertensives ranged from 6% (T0+A10) to 25% (T40+A0).

DBP100

Results for the DBP100 subset were consistent with those observed for the FAS. At the end of treatment, the proportions of patients with optimal, normal, or high normal BP in the key combination therapy groups of the DBP100 subset ranged from 54% (T40+A5) to 77% (T80+A10) and were considerably higher than in the placebo group (11%) and than in the

monotherapy groups where between 33% (T0+A5) to 52% (T0+A10) were controlled at the end of the trial. The proportion of patients with Grade 2/3 hypertension ranged from 2% to 8% for the key combination groups compared with 8% (T0+A10) to 29% (T40+A0) for monotherapy and 54% for placebo treatment.

Blood pressure control rates over time

FAS

The DBP control rate improved over time with increasing doses of telmisartan and amlodipine as monotherapy and in combination. The percentage of patients with DBP control was consistently higher in the 4 key combination treatment groups than in their respective monotherapy groups. Higher control rates were already apparent after 2 weeks of treatment for the 4 key combination treatment groups (57% to 63%) compared to the respective monotherapies (39% to 51%) showing that initial therapy with the combination treatments resulted in more rapid DBP control. Most of the effect was achieved within the initial 4 weeks, despite the initial 2-week forced titration for amlodipine in the 10 mg treatment groups. At the end of the 8-week treatment period, control rates ranged from 72% (T40+A5) to 85% (T80+A10) in the 4 key combination treatment groups and from 53% (T0+A5) to 73% (T0+A10) in the respective monotherapy groups; the control rate in the placebo group was 30%.

SBP control rates increased over time and with dosage in the combination treatment groups. Control rates in the 4 key combination treatment groups were consistently higher than in the respective monotherapy groups at all time points. A treatment effect was already apparent after 2 weeks of treatment, when all 4 key combination treatments had at least 62% of patients having achieved SBP control; this proportion increased further over the remaining weeks, and approached the maximum observed antihypertensive effect after 4 weeks. At the end of trial, control rates ranged from 73% (T40+A5) to 87% (T40+A10) across the 4 key treatment combination groups and were greater than those observed in the respective monotherapy groups (range 56% (T40+A0) to 77% (T0+A10)); the control rate was 28% in the placebo group.

DBP100 and Grade 2/3 subset

DBP and SBP control rates over time in the DBP100 subset showed a similar pattern to that observed in the FAS. Control rates increased over time and with dosage, and were consistently higher in the 4 key combination treatment groups than in the respective monotherapies.

Probability of achieving blood pressure control depending on baseline BP

Results showed that combination therapy is associated with a statistically and clinically significantly greater likelihood of meeting BP goals of SBP <140 mmHg, DBP <90 mmHg, and both concomitantly, than the respective monotherapies. The results of the probability of achieving DBP control at the end of trial using the criteria of <90 mmHg are presented for the 4 key combination treatment groups and their respective monotherapy components in Table 21. Regardless of the DBP criteria (that is, DBP <90 mmHg or DBP <80 mmHg) in all cases, combination therapy was associated with a higher probability of achieving DBP control than the individual monotherapies; odds ratios were consistently in favour of the key combination therapies. Additionally, a higher probability is seen for the 4 pooled key combination treatment groups (T40+A5, T40+A10, T80+A5, T80+A10) than for the respective pooled telmisartan monotherapies (T40, T80) and pooled amlodipine monotherapies (A5, A10).

Table 21: Probability of achieving DBP control (<90 mmHg) at end of trial 1235.1* adjusted for baseline DBP for key combination treatment groups and respective monotherapies, including odds ratios between treatments

Characteristic	Key combination	Telmisartan monotherapy	Amlodipine monotherapy
Treatment (number of patients, N)	T40+A5 (141)	T40 (129)	A5 (137)
Probability of DBP <90 mmHg	**0.72**	**0.55**	**0.57**
95% CI	(0.64–0.79)	(0.46–0.64)	(0.47–0.66)
Comparison vs T40+A5			
Odds ratio	–	2.09	1.98
95% CI	–	(1.23–3.54)	(1.15–3.40)
p-value	–	0.0062	0.0136
Treatment (number of patients, N)	T40+A10 (123)	T40 (129)	A10 (124)
Probability of DBP <90 mmHg	**0.84**	**0.55**	**0.75**
95% CI	(0.75–0.89)	(0.46–0.64)	(0.65–0.83)
Comparison vs T40+A10			
Odds ratio	–	4.09	1.68
95% CI	–	(2.20–7.60)	(0.85–3.33)
p-value	–	<0.0001	0.1355
Treatment (number of patients, N)	T80+A5 (143)	T80 (132)	A5 (137)
Probability of DBP <90 mmHg	**0.77**	**0.61**	**0.57**
95% CI	(0.69–0.84)	(0.52–0.69)	(0.47–0.66)
Comparison vs T80+A5			
Odds ratio	–	2.22	2.61
95% CI	–	(1.27–3.88)	(1.47–4.64)
p-value	–	0.0050	0.0010
Treatment (number of patients, N)	T80+A10 (136)	T80 (132)	A10 (124)
Probability of DBP <90 mmHg	**0.85**	**0.61**	**0.75**
95% CI	(0.78–0.90)	(0.52–0.69)	(0.65–0.83)
Comparison vs T80+A10			
Odds ratio	–	3.75	1.92
95% CI	–	(2.05–6.86)	(0.98–3.74)
p-value	–	<0.0001	0.0563
Pooled treatments (number of patients, N)	Key combinations (543)	T40, T80 (261)	A5, 10 (261)
Probability of DBP <90 mmHg	**0.79**	**0.58**	**0.66**
95% CI	(0.75–0.83)	(0.52–0.64)	(0.59–0.72)
Comparison vs 4 pooled key combinations			
Odds ratio	–	2.77	2.01
95% CI	–	(1.97–3.87)	(1.39–2.89)
p-value	–	<0.0001	0.0002

* Missing values replaced by LOCF.
Note: For calculation of odds ratios placebo was excluded.

The probability of achieving SBP control using the criteria of <140 mmHg and <130 mmHg at the end of trial is presented for the 4 key combination treatment groups and their respective monotherapy components was also presented. Regardless of the SBP criteria, in all cases combination therapy was associated with a higher probability of achieving SBP control than the individual monotherapies; odds ratios were consistently in favour of the key combination treatments.

Results from the ABPM substudy

A total of 562 (38.5%) of the 1461 randomised and treated patients in trial 1235.1 were included in the ABPM substudy; 403 of these patients had moderate or severe hypertension at baseline. Patients in this substudy had ABPM assessments performed at their baseline. Hourly DBP and SBP values were summarised relative to dosing time and calculations based

on these data were performed to determine the 24 hour mean DBP and SBP for each treatment group.

FAS

The mean 24 hour mean DBP and SBP values obtained by ABPM were calculated based on the hourly means, relative to dosing time and tabulations for values at baseline, at end of trial, and change from baseline. The 24-hour mean of the hourly BP values obtained by ABPM decreased monotonically with increasing doses of either monotherapy or combination therapy. ABPM provides a much denser set of BP data than in-clinic cuff BPs, and these results are quite robust albeit having been obtained in a group of about half the evaluated patients. The 24-hour mean DBP changes from baseline ranged from –11.0 to –14.6 mmHg in the 4 key treatment combination groups. This compared with changes ranging from –5.4 to –6.9 mmHg in the respective monotherapy treatment groups and –0.3 mmHg for the placebo group. An increasing overall reduction with increasing dosage of both telmisartan and amlodipine was also found for the changes from baseline in the 24-hour mean SBP. The mean reductions in the T40+A5 and T80+A5 groups were considerably greater than those in the full-dose A10 group. These data clearly show the dose-response and additive effect of combination therapy.

DBP100

As with the FAS, the magnitude of overall reductions increased with increasing dosage of telmisartan and increasing dosages of amlodipine in the DBP100 subset. The 24-hour mean DBP changes from baseline ranged from –11.0 to –15.3 mmHg in the 4 key combination treatment groups. This compared to changes ranging from –5.0 to –7.3 mmHg in the respective monotherapy treatment groups and –1.3 mmHg for the placebo group. The 24-hour mean SBP changes from baseline ranged from –16.7 to –22.7 mmHg in the 4 key combination treatment groups as compared with changes from –7.4 to –12.2 mmHg in the respective monotherapy treatment groups and –3.0 mmHg for the placebo group. The mean reductions in the T40+A5 and T80+A5 groups were considerably greater than those in the full-dose A10 group.

Incidence of oedema

FAS

The reported incidence rates were 9.1% for patients who received amlodipine monotherapy, 0.7% for patients who received telmisartan monotherapy, and 6.1% for patients who received T+A combination therapy. There were no reported cases of oedema in the placebo group. The majority of the cases of oedema (61 patients) occurred in the A10 treatment groups and the highest incidence was found in patients who received A10 monotherapy (20.2%). Incidences in the key combination treatment groups with A10 were 9.8% (T40+A10) and 14.0% (T80+A10). Incidences in the other key combination treatment groups and the monotherapy groups were all below 3%.

DBP100

The incidences of oedema in the DBP100 subset were similar to those in the FAS. Oedema was reported in 51 patients in the DBP100 subset. The reported incidence rates were 8.6% for patients who received amlodipine monotherapy, 0.9% for patients who received telmisartan monotherapy, and 5.2% for patients who received T+A combination therapy. As in the FAS, the majority of cases (39 patients) occurred in the A10 treatment groups, with the highest incidence in the A10 monotherapy group (19.3%). Incidences in the 2 key combination

treatment groups with A10 were 9.4% (T40+A10) and 11.0% (T80+A10). Incidences in the 2 other key combination treatment groups and monotherapy groups were all below 3%.

Grade 2/3 subset

Oedema was reported in 59 patients in the Grade 2/3 subset and the overall profile across the treatment groups was similar to that in the FAS and the DBP100 subset.

Subgroup analyses

Age

FAS

Since the majority of patients within each treatment group were <65 years of age, comparison across age categories was difficult. Generally, efficacy appeared similar, or somewhat greater, in patients over 65 years of age than in those <65 years of age. The antihypertensive effect was greater in each key combination treatment group than in the respective monotherapy treatment groups for each age category.

SBP efficacy appeared similar, or somewhat greater, in patients≥65 years of age when compared to those <65 years of age.

DBP100 and Grade 2/3 subsets

Results for the age subgroups in the DBP100 and Grade 2/3 subsets of trial 1235.1 were similar to those in the FAS.

Gender, BMI

Reductions of BP were greater in the combination treatment groups than in the monotherapy groups in both men and women. Mean changes in DBP and SBP were only slightly higher in women than in men, and the differences were not likely to be clinically relevant.

Results were analysed for patients with BMI≥30 kg/m² and with BMI <30 kg/m². There was no consistent pattern of differences in BP reductions in patients with BMI < or ≥30 kg/m², and no changes were clinically relevant.

Evaluators comment

Trial 1235.1 was appropriately designed and conducted to evaluate first line combination therapy with telmisartan and amlodipine in the treatment of hypertension. Guidelines including the ESH/ESC guidelines published in 2007, the TGA-adopted EU guidance on the treatment of hypertension and the draft EU CPMP/EWP/238/95 Rev 3 describe the clinical need and the requirements for first line combination therapy in the treatment of hypertension in patients with high cardiovascular risk, for example patients with moderate to severe hypertension. Data from trial 1235.1 showed superior BP-lowering effect and demonstrated that each component made a contribution within the fixed combination.

Therapy with the 4 key combinations demonstrated significantly larger DBP and SBP reductions compared to each monotherapy component in the overall population. Both amlodipine low-dose combinations (T40+A5 and T80+A5) showed comparable or larger BP reductions than the full-dose monotherapies (A10 andT80).

The BP goal was achieved in a more timely fashion after initial therapy with amlodipine low-dose combinations than with full-dose monotherapies. In addition, higher DBP control rates were observed at the earliest visit after 2 weeks but also at the end of the trial. Combination therapy, in general, resulted in consistently higher BP control rates after already 2 weeks of

treatment and higher probabilities of achieving the BP goal compared to the respective monotherapies.

Although trial 1235.1 also investigated dosages of 2.5 mg amlodipine (A2.5) and 20 mg telmisartan (T20), the 2.5 mg dose of amlodipine is not commercially available in Australia and the combinations were less efficacious than the A5 and A10 combinations. The T20 combinations were less efficacious than the T40 and T80 combinations and a significant difference compared to the respective monotherapies could not be demonstrated for all T20 combinations and parameters.

Supportive studies

Trials 1235.7 and 1235.8

Patients who completed 8 weeks of randomised treatment in trial 1235.5 or 1235.6 were offered the option of receiving open-label treatment with the FDCs of T/A for up to 34 weeks in trial 1235.7 or 1235.8, respectively. Completion of trial 1235.5 or 1235.6 had to take place in the 14 days before Visit 1 of the follow-up trial. In the case of inadequate control (DBP ≥90 mmHg), additional antihypertensive therapy (excluding ARBs or dihydropyridine CCBs) was to be given. BP measurements were scheduled at Weeks 4, 8, 18, 22, and 34 (end of trial).

In trial 1235.7, all patients initially received T40/A5. If BP goals were not achieved with T40/A5 at Week 4 or 8, the dose was to be up-titrated to T80/A5. After Week 8, up-titration from T40/A5 to T80/A5 was not foreseen in the protocol, that is, patients who were on T40/A5 but not controlled beyond Week 8 were to receive an additional antihypertensive agent at subsequent visits instead of up-titration from T40/A5 to T80/A5. In patients who were up-titrated at Week 4, additional antihypertensive treatment was allowed after a further 4 weeks (Week 8). The long-term efficacy of the T40/A5 and T80/A5 FDCs was evaluated when given alone or in combination with other antihypertensive treatments.

In trial 1235.8, all patients initially received T40/A10 for a 4-week run-in period and were then randomised in a 3:2 ratio to treatment with T80/A10 or T40/A10. After a further 4 weeks (at Week 8), patients randomised to T40/A10 were up-titrated to T80/A10 if they had not attained their BP goal (DBP <90 mmHg). After Week 8, up-titration from T40/A10 to T80/A10 was not foreseen but additional antihypertensive therapy was recommended if DBP control was inadequate at the following visits. In patients randomised to treatment with T80/A10 at Week 4, additional antihypertensive therapy was recommended if DBP control was inadequate from Week 8 on. The long-term efficacy of the T40/A10 and T80/A10 FDCs was evaluated when given alone or in combination with other antihypertensive treatments.

Main inclusion criteria

Adult patients with essential hypertension and uncontrolled BP at the start of run-in (defined as sDBP ≥95 mmHg in patients treated with antihypertensives and DBP ≥100 mmHg in patients not treated with antihypertensives) were enrolled. Patients on open-label A5 monotherapy were randomised if they did not respond adequately (defined as DBP≥90 mmHg) after 6 weeks of treatment.

Trial endpoints

For trial 1235.7 there were 2 co-primary endpoints, the change from baseline in trough sDBP and the incidence of oedema during the double-blind phase.

Secondary endpoints were trough seated systolic blood pressure (SBP); proportions of patients achieving DBP and SBP control, DBP and SBP response; proportions of patients with optimal, normal, high-normal BP, Stage-I, and Stage-II hypertension.

For trial 1235.8 the primary endpoint was the change from baseline in trough sDBP. Secondary endpoints were the change from baseline trough seated systolic blood pressure (SBP), proportions of patients achieving trough DBP / SBP control, trough DBP / SBP response, proportions of patients with optimal, normal, high-normal BP, Stage 1, and Stage 2 hypertension, and incidence of oedema.

Patient disposition

Trial 1235.7

A total of 965 (93.9%) of the 1028 patients who completed trial 1235.5 entered the open-label follow-up trial 1235.7. All patients were to receive T40/A5 in the first 4 weeks of trial 1235.7. Patients who showed inadequate BP control (defined as DBP ≥90 mmHg) at Week 4 or 8 were up-titrated to the higher strength FDC of T80/A5. At subsequent visits (Weeks 8, 14 and 22), up-titration from T40/A5 to A80/A5 was not allowed but additional antihypertensive therapy (excluding ARBs and dihydropyridine CCBs) was to be added if DBP control was inadequate.

Of the 965 patients who entered the trial, 578 (59.9%) remained on the low-dose T40/A5 FDC throughout the trial. Only 25 (4.3%) of these 578 patients received additional antihypertensives at or after Week 14 (T40/A5+). A total of 387 (40.1%) out of the 965 patients who entered the trial were up-titrated to the higher dose strength of T80/A5 at Week 4 or 8. 181 (46.8%) of the 387 patients on T80/A5 received additional antihypertensives Week 8 or 14 onwards (T80/A5+).

Overall, 929 (96.3%) of the 965 patients completed trial 1235.7 and 36 (3.7%) patients discontinued prematurely. 21 (2.2%) patients discontinued due to administrative reasons and 15 (1.6%) patients due to the occurrence of AEs.

Trial 1235.8

The open-label follow-up trial 1235.8 was still ongoing at the time of the submission and results are based on an interim analysis (database lock 9 April 2009). All patients were included who were enrolled in the trial (had Visit 1) on or before 31 July 2008; at this time point 436 (48.8%) of the 894 patients who had completed trial 1235.6 (FAS) had entered trial 1235.8. All patients were to receive T40/A10 in the first 4 weeks of trial 1235.8. At Week 4, patients were randomised to T80/A10 and T40/A10 in a ratio of 3:2. Patients randomised to T80/A10 who showed inadequate BP control (defined as DBP ≥90 mmHg) at visits from Week 8 onwards were to be given additional antihypertensive therapy. Patient randomised to T40/A10 continued at this dose as long as their DBP was adequately controlled but those patients with inadequate DBP control at Week 8 were up-titrated to T80/A10. Patients randomised to T40/A10 and not up-titrated at Week 8 but with inadequate DBP control at visits from Week 14 onwards were to be given additional antihypertensive therapy.

Of the 436 patients who entered the trial, 123 (28.2%) remained on the low-dose FDC T40/A10 throughout the trial. Only 6 (4.9%) of these 123 patients received additional antihypertensives at or after Week 14 (T40/A10+). A total of 313 (71.8%) out of the 436 patients (FAS) who entered the trial were treated with the higher dose strength of T80/A10. 258 of these patients were randomised to T80/A10 at Week 4 and 55 patients were up-titrated based on their response from T40/A10 to the higher dose at Week 8. 61 (19.5%) of the 313 patients on T80/A10 received additional antihypertensives from Week 8 onwards (T80/A10+).

Overall, 421 (96.6%) of the 436 patients completed trial 1235.8 and 15 (3.4%) patients discontinued prematurely. 8 (1.8%) patients discontinued due to the occurrence of AEs, 5 (1.1%) due to administrative reasons, and 2 (0.5%) due to other reasons.

Demographics and baseline data

The demographic characteristics in the open-label follow-up trials 1235.7 and 1235.8 were recorded at the beginning (screening visit) of the preceding trials 1235.5 and 1235.6,

respectively. As expected, the overall demographic characteristics in the FAS of the follow-up trials were similar to those in the preceding trials.

Within each trial, the characteristics of the underlying hypertension showed some differences between the treatments. In trial 1235.7, patients who had an inadequate response to T40/A5 and were up-titrated to T80/A5 had more severe baseline disease than patients who remained on T40/A5 throughout the trial: mean durations of hypertension in the T80/A5+ and T80/A5 treatments were longer than in the T40/A5+ and T40/A5 treatments, baseline SBP and DBP were higher, and larger proportions of patients had Grade 2 or 3 hypertension. Within each of the 2 dose levels, baseline hypertension was more severe in patients who required additional antihypertensive medication than in those who did not. As expected, the patients in the T80/A5+ group had the most severe baseline hypertension (for example, mean duration of hypertension 7.2 years vs 5.1 to 5.9 years in the 3 other treatments, proportion of patients with Grade 2 or 3 hypertension 61.3% vs 24.0% to 42.2%).

In trial 1235.8, some differences were observed between the treatments but most of them were not considered to be clinically relevant either due to the small population size (T40/A10+, N=6) or the fact that most of the patients were assigned to the high-dose group by randomisation (and not as a result of up-titration). However, within the T80/A10 dose level, results indicated that baseline hypertension was more severe in patients who required additional antihypertensive medication than those who did not: baseline SBP and DBP and frequencies of patients with Grade 2 hypertension were higher in the T80/A10+ group than the T80/A10 group.

Within each trial baseline characteristics were generally well balanced across the treatments. In trial 1235.7, however, there were some differences: the proportion of patients with a history of smoking ranged from 33.5% (T80/A5) to 60.0% (T40/A5+); the proportion of patients who reported use of alcohol was higher in patients with T40/A5 as final treatment (39.1%) than in the other treatments (24.0% to 31.1%); the proportions of patients with BMI ≥30 kg/m² were lower in the T40/A5+ and T40/A5 groups (28.0% and 32.9%) than in the T80/A5+ and T80/A5 groups (44.2% and 44.7%).

Efficacy results

Blood pressure over time in trial 1235.7

The overall mean reduction of trough sDBP between baseline of trial 1235.5 and the final visit of trial 1235.7 was 13.0 mmHg (Table 22). The majority of this reduction (8.5 mmHg) occurred during the 8 weeks of double-blind treatment in the preceding trial 1235.5. However, DBP continued to decrease during the first 14 weeks of open-label treatment in trial 1235.7, with mean reductions with respect to baseline of trial 1235.5 of 10.8 mmHg after 4 weeks, 12.2 mmHg after 8 weeks, and 13.1 mmHg after 14 weeks. The mean reduction in DBP was maintained from Week 14 onwards.

Table 22: Change in mean trough seated DBP [mmHg] over time in trial 1235.7 by actual treatment (FAS)

Timepoint	T40/A5		T80/A5		T40/A5+		T80/A5+		Total	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline *									952	96.7 (5.0)
End of trial 1235.5									952	88.1 (8.6)
Change in trial 1235.5									940	–8.5 (7.8)
Change from baseline in trial 1235.7 *										
Week 4	924	–10.8 (7.8)							931	–10.8 (7.8)
Week 8	626	–13.7 (7.4)	304	–9.2 (7.7)	1	–14.7			931	–12.2 (7.7)
Week 14	559	–14.4 (7.0)	249	–11.7 (7.4)	1	–5.3	111	–9.8 (6.9)	921	–13.1 (7.3)
Week 22	532	–14.4 (7.3)	201	–12.9 (6.7)	14	–8.6 (8.2)	157	–10.4 (8.0)	906	–13.3 (7.4)
Final individual visit	549	–14.2 (7.3)	202	–12.7 (6.9)	24	–9.5 (5.5)	177	–10.2 (8.1)	952	–13.0 (7.5)

* Baseline is defined as the randomisation visit (Visit 3) in trial 1235.5. It should be noted that 13 of the 965 patients in the FAS of trial 1235.7 did not have baseline BP values.

At the final visit, 60.2% patients (573/952) were still receiving T40/A5 and 39.8% patients (379/952) had been up-titrated to T80/A5. Only 4.2% of the patients (24/573) on T40/A5 had received additional hypertensive therapy compared with 46.7% (177/379) of the patients on T80/A5. At the final visit, the highest mean reduction from baseline in DBP was found in the T40/A5 group (14.2 mmHg). As expected, the reductions both in this group and the T80/A5 group (12.7 mmHg) were higher than those in the groups receiving additional antihypertensive medication (T40/A5+ 9.5 mmHg, T80/A5+ 10.2 mmHg) indicating that patients in these groups are difficult to treat, even with a combination therapy.

The overall mean reduction of trough sSBP between baseline of trial 1235.5 and the final visit of trial 1235.7 was 16.6 mmHg. As for DBP, the majority of this reduction (11.6 mmHg) occurred during the preceding trial 1235.5. SBP continued to decrease during the first 14 weeks of open-label treatment in trial 1235.7, with mean reductions with respect to baseline of trial 1235.5 of 13.8 mmHg after 4 weeks, 15.5 mmHg after 8 weeks, and 16.7 mmHg after 14 weeks. At the final visit, the highest mean reduction in SBP was found in the T40/A5 group (17.8 mmHg). Reductions both in this group and the T80/A5 group (15.9 mmHg) were higher than those in the groups receiving additional antihypertensive medication (T40/A5+ 12.6 mmHg, T80/A5+ 14.1 mmHg).

Blood pressure over time in trial 1235.8

The general pattern of mean DBP and SBP changes in trial 1235.8 was similar to that in trial 1235.7 (Table 23). The overall mean reduction of trough sDBP between baseline of trial 1235.6 and the final visit of trial 1235.8 was 12.6 mmHg. The majority of this reduction (8.2 mmHg) occurred during the 8 weeks of double-blind treatment in the preceding trial 1235.6. DBP continued to decrease during the first 14 weeks of open-label treatment in trial 1235.8, with mean reductions from baseline of trial 1235.6 of 9.8 mmHg after 4 weeks, 11.0 mmHg after 8 weeks, and 12.3 mmHg after 14 weeks. The mean reduction in DBP was maintained from Week 14 onwards.

Table 23: Change in mean trough seated DBP [mmHg] over time in trial 1235.8 by actual treatment (FAS)

Timepoint	T40/A10		T80/A10		T40/A10+		T80/A10+		Total	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline *									436	95.7 (3.9)
End of trial 1235.6									430	87.4 (7.1)
Change in trial 1235.6									430	–8.2 (6.8)
Change from baseline in trial 1235.8 *										
Week 4	426	–9.8 (7.1)							427	–9.8 (7.1)
Week 8	175	–10.0 (6.8)	249	–11.9 (6.6)					426	–11.0 (6.8)
Week 14	120	–13.2 (5.5)	281	–12.2 (6.8)	2	–18.7 (1.9)	24	–9.3 (6.1)	428	–12.3 (6.5)
Week 22	114	–12.7 (5.8)	254	–12.7 (6.1)	4	–16.5 (6.9)	46	–10.3 (7.2)	420	–12.4 (6.2)
Final individual visit	117	–12.9 (6.5)	252	–12.8 (6.1)	6	–10.8 (10.0)	61	–11.1 (6.3)	436	–12.6 (6.3)

* Baseline is defined as the randomisation visit (Visit 4) in trial 1235.6.

At the final visit of trial 1235.8, 71.8% (313/436) of patients were receiving T80/A10 and 28.2% (123/436) were receiving T40/A10. Only 4.9% (6/123) of the patients treated with T40/A10 at the final visit received additional hypertensive therapy compared with 19.5% (61/313) of the patients treated with T80/A10. At the final visit, similar mean reductions in DBP were found in the T40/A10 and T80/A10 groups (12.9 and 12.8 mmHg, respectively).

It should be noted that the T80/A10 group comprises patients who were randomised to T80/A10 and patients who were up-titrated to T80/A10 due to inadequate response. Reductions in the groups receiving additional antihypertensive medication were lower (T40/A10+ 10.8 mmHg, T80/A10+ 11.1 mmHg).

The overall mean reduction of trough sSBP between baseline of trial 1235.6 and the final visit of trial 1235.8 was 14.7 mmHg. As for DBP, the majority of this reduction (9.8 mmHg) occurred during the preceding trial 1235.6. SBP continued to decrease during the first 14 weeks of open-label treatment in trial 1235.8, with mean reductions with respect to baseline of trial 1235.6 of 11.4 mmHg after 4 weeks, 13.2 mmHg after 8 weeks, and 14.2 mmHg after 14 weeks. At the final visit, clinically relevant mean reductions were found in patients treated with T40/A10 or T80/A10 (14.4 and 15.4 mmHg, respectively). Reductions in the patients receiving additional antihypertensive medication were lower (T40/A10+ 12.8 mmHg, T80/A10+ 12.4 mmHg).

Blood pressure control and response rates over time in trial 1235.7

The overall rates for the total population showed a consistent pattern. Although the majority of patients already displayed adequate BP control (54.8% DBP, 55.4% SBP) or response (60.6% DBP, 59.7 SBP) at the end of trial 1235.5, control and response rates gradually increased during open-label treatment in trial 1235.7 up until Week 14. Rates at Week 22 were similar to those at Week 14. At the final visit of trial 1235.7, 79.5% patients had achieved DBP control, 84.0% DBP response, 71.2% SBP control, and 76.2% SBP response. In the case of SBP control and response, rates at the final visit were similar to those at Week 22. However, in the case of DBP control and response, rates at the final visit were generally slightly lower than those at Week 22. The reason for the lower rates is unclear.

Distributions of control and response rates at the final visit differed across the treatments. The highest rates occurred in patients treated with T40/A5, followed by those treated with T80/A5. For each dose level, the rate in patients receiving additional hypertensive medication was lower than that in patients without hypertensive medication.

Blood pressure control and response rates over time in trial 1235.8

The overall rates for the total population showed a consistent pattern consistent with the results found in trial 1235.7. The majority of patients already displayed adequate BP control (61.6% DBP, 54.7% SBP) or response (64.0% DBP, 58.4% SBP) at the end of trial 1235.6,

rates gradually increased during open-label treatment in trial 1235.8 up until Week 14. Rates at Week 22 were similar to those at Week 14. At the final visit of trial 1235.8, 88.1% patients had achieved DBP control, 89.9% DBP response, 75.9% SBP control, and 79.8% SBP response.

Control and response rates at the final visit differed across the treatment groups. The highest rates occurred in the T40/A10 group, followed by the T80/A10 group. Again it should be noted that this latter group also not only included patients who were randomised to T80/A10 but also patients who were up-titrated due to inadequate response defined as those patients who were more difficult to treat. In line with this, rates in patients receiving additional hypertensive medication were lower than those in corresponding groups without hypertensive medication.

Blood pressure categories over time in trial 1235.7

The overall proportions of patients with optimal, normal or high normal BP increased during trial 1235.5 and from the end of trial 1235.5 up until Week 8 (optimal, normal) or Week 14 (high normal) of trial 1235.7. The rates for patients with Grade 1 or Grade 2 hypertension decreased correspondingly. Very few patients had Grade 3 hypertension.

At the final visit of trial 1235.7, the majority of patients (63.0%, 608/965) had optimal, normal, or high normal BP compared with only 0.1% at baseline; 32.3% and 4.5% had Grade 1 and Grade 2 hypertension, respectively. The T40/A5 group contained higher proportions of patients with optimal or normal BP than the 3 other treatment groups and a lower proportion of patients with Grade 1 hypertension.

Blood pressure categories over time in trial 1235.8

The overall proportions of patients with optimal, normal or high normal BP increased during trial 1235.6 and from the end of trial 1235.6 up until Week 14 (optimal, high normal) or Week 22 (normal) of trial 1235.8. The rates for patients with Grade 1 or Grade 2 hypertension decreased correspondingly. Only 1 patient had Grade 3 hypertension. While at baseline no patient had optimal, normal or high normal BP, the majority (72.9%, 318/436) of patients had optimal, normal, or high normal BP at the final visit of trial 1235.8; 25.2% and 1.6% had Grade 1 and Grade 2 hypertension, respectively.

The frequencies of BP categories in the T40/A10 group were generally similar to those in the T80/A10 group. At the final visit of trial 1235.8, the majority of patients in these groups had either normal BP (about 35%) or high normal BP (about 40%); about 20% had Grade 1 hypertension.

Effect of up-titration on blood pressure

Analyses were performed to investigate the effect of increasing the telmisartan dose in the T/A FDC from T40 to T80 during open-label follow-up treatment in trials 1235.7 and 1235.8 and to see if an additional effect in terms of BP reduction could be maintained over time.

In trial 1235.7 the dose was up-titrated from T40/A5 to T80/A5 at Weeks 4 and 8 if DBP control was inadequate; this took place in 390 (40.4%) of the 965 patients in the FAS. Up titration took place after treatment duration of a mean of 38.3 days on T40/A5 and led to a decrease in BP that was maintained at the last dose of treatment. Mean SBP/DBP decreased from 145.5/94.6 mmHg at the last visit on T40/A5 to 140.0/89.4 mmHg at the first visit on T80/A5 after treatment duration of a mean of 34.2 days. Control rates increased from 5.4% to 54.1% for DBP <90 mmHg and from 31.3% to 51.0% for SBP control <140 mmHg. Response rates increased from 22.1% to 65.4% for DBP and from 36.9% to 57.4% for SBP. The proportion of patients with optimal, normal or high normal BP increased from 2.6% to

37.7%. Values at the last visit on T80/A5, which was on average 117.9 days after start of up-titration, were similar to those at the first visit on T80/A5.

In trial 1235.8, the dose was increased from T40/A10 to T80/A10 in 313 (71.8%) of the 436 patients in the FAS either as a result of randomisation at Week 4 (258 patients) or up-titration due to inadequate DBP control at Week 8 (55 patients).

Randomisation accounted for the higher proportion of patients on the high dose T/A FDC compared with trial 1235.7 (40.4%). Increasing the dose from T40/A10 to T80/A10 led to a decrease in BP that was maintained until the last dose of treatment.

The mean SBP/DBP decreased from 138.0/87.0 mmHg at the last visit on T40/A10 to 134.9/84.6 mmHg at the first visit on T80/A10 (by 3.1/2.4 mmHg). A larger BP reduction of 5.2/4.3 mmHg was observed in the patients who were up-titrated due to inadequate DBP control.

Control rates increased from 56.3% to 81.3% for DBP <90 mmHg and from 53.3% to 64.5% for SBP control <140 mmHg. Response rates increased from 61.8% to 82.9% for DBP and from 55.9% to 69.7% for SBP. The proportion of patients with optimal, normal or high normal BP increased from 42.1% to 59.2%. Values at the last visit on T80/A10 were similar to those at the first visit on T80/A10. In general, the changes between the last visit on the low-dose combination and the first visit on the high-dose combination in trial 1235.8 were smaller than in trial 1235.7. This can be expected due to the higher amlodipine dose in trial 1235.8.

Incidence of oedema

The proportion of patients with oedema increased slightly from 8.5% (82/965 patients) at the end of trial 1235.5 to 13.7% (132/962) at the end of trial 1235.7 A similar increase was seen from 10.3% (45/436 patients) at the end of trial 1235.6 to 15.4% (67/434) at the end of trial 1235.8. The new cases of oedema did not show any pattern of distribution with regard to either time or treatment.

Evaluator's overall conclusions on clinical efficacy

In this application the sponsor provided data to support the use of 4 telmisartan and amlodipine FDC dose strengths (T40/A5, T40/A10, T80/A5 and T80/A10) for the treatment of hypertension, both as add on therapy in patients not adequately controlled on antihypertensive amlodipine therapy, and as initial therapy in patients likely to need multiple drugs to achieve their BP goals.

Add-on therapy

Trials 1235.5 and 1235.6 were the pivotal trials investigating the efficacy of the T/A FDCs in hypertensive patients who did not respond adequately to 6 weeks of A5 or A10 monotherapy. In trial 1235.5, T80/A5 and T40/A5 were statistically superior not only to continuing treatment with A5 but also to increasing the amlodipine dose from 5 mg to the maximum registered dose of 10 mg. In trial 1235.6, T80/A10 and T40/A10 were superior to continuing treatment with A10. The combination treatments also resulted in significantly larger reductions of trough sSBP compared to amlodipine monotherapy. These observed reductions in DBP obtained in amlodipine non-responders are considered clinically relevant as described in recent publications and guidelines. Analyses of mean BP changes over time showed that the most of the reduction in DBP and SBP was already apparent within 4 weeks of treatment.

Analyses of the secondary categorical BP endpoints (DBP and SBP control, DBP and SBP response, BP categories) and probabilities of achieving BP control depending on baseline BP

supported the analyses of changes in DBP and SBP. For all endpoints the T80/A5 and T40/A5 groups showed better efficacy than the A5 group; the same was true for the T80/A10 and T40/A10 groups compared to the A10 group. T80/A5 was consistently more efficacious than A10 and T40/A5 displayed at least numerically better BP effects than A10 for most efficacy variables.

In trial 1235.5 (A5 non-responders), the incidence of oedema for the pooled T/A groups was significantly lower (both statistically and clinically) than when amlodipine was up-titrated to A10 demonstrating the superiority of the combination treatment for both BP reductions and less oedema. In trial 1235.6 (A10 non-responders), the rate of oedema was generally comparable across the treatment groups but fewer patients on combination therapy discontinued due to oedema than on A10 monotherapy.

Results of subgroup analyses by age (<65/≥65 years), sex (male/female), B MI category (<30/≥30 kg/m²), did not reveal any notable differences in efficacy.

These efficacy results adequately support the use of T/A combination therapy at dose strengths of T40/A5, T40/A10, T80/A5 and T80/A10 once daily to treat hypertension in patients who do not respond adequately to treatment with amlodipine monotherapy at either of the daily recommended doses of 5 or 10 mg.

Initial therapy

Trial 1235.1 was performed in patients with DBP at baseline≥95 mmHg and ≤119 mmHg, of whom 79% (1129/1423) were moderate to severe hypertensives. The trial design and patient population was appropriate to assess first line use of the FDC.

All 4 T+A key combination dose strengths showed superior efficacy compared to the respective monotherapies in the FAS after 8 weeks. The majority of the antihypertensive effect was attained within 2 weeks and close to the maximum observed antihypertensive effect that was observed within 4 weeks. The 4 key T+A combination treatment groups also attained greater BP reductions at 2 weeks compared to the monotherapy groups. Increasing doses of each component of the FDC produced incremental BP changes from baseline. Consistent with these results, DBP control rates increased over time, and with dosage, and were consistently higher in combination treatment than in the respective monotherapies. In the T+A combination groups, greater rates of control (SBP and DBP) were noted at 2 weeks compared to the monotherapy groups. For the measures of DBP control (sDBP <90 mmHg) and DBP response (sDBP <90 mmHg or reduction from baseline≥10 mmHg), the highest proportions of patients were observed in the T80+A10 treatment group and the highest proportion of patients who qualified at the end of trial for the hypertensive classes of 'BP optimal' (BP <120/80 mmHg) and 'BP normal' (BP <130/85 mmHg but not optimal) was also in the T80+A10 group.

Superiority of combination compared to monotherapy treatment was further supported by the probability analyses for achievement of BP control in dependence of baseline BP. Further analyses were performed in 2 subsets of patients with moderate to severe hypertension at baseline (DBP100 subset, Grade 2/3 subset), that is, in patients in whom, according to current guidelines, combination therapy should be considered as first choice. Similar results to those reported for the overall population were observed for these groups of patients. Significantly greater reductions in DBP and SBP were noted with combination therapy than with monotherapy. Additionally, more rapid reductions in BP with greater SBP and DBP control rates were noted for the T+A combination groups compared to the T and A monotherapy groups, providing further support for the use of initial therapy with T40/A5 and T80/A5 combinations.

The regulatory requirements if first line therapy is claimed for a fixed low-dose combination were discussed in the Introduction to Section IV on pages 16-17. These included:

1. Each substance (component) has a documented contribution within the (fixed) combination

The use of a FDC containing telmisartan and amlodipine as first line treatment for hypertensive patients likely to need multiple drugs to achieve BP goals is appropriate given the efficacy results for the DBP100 and Grade 2/3 subsets in trial 1235.1.

BP reductions were better for all key combination treatment groups than for the respective monotherapies. Even with the combinations containing low-dose amlodipine (A5), comparable or better BP reductions were observed in the moderate to severe subsets combined with a significantly lower rate of oedema than with high-dose amlodipine (i.e. A10). Furthermore, higher control rates were achieved earlier and time until DBP control was shorter in patients treated with the key combinations compared to those treated with the respective monotherapies. This was the case even for patients treated with the low-dose combination (T40+A5) compared to those treated with full-dose amlodipine monotherapy (A10).

In relation to the guidelines it was demonstrated that each substance (component) has a documented contribution within the (fixed) combination. It therefore fulfils one requirement according to the TGA-adopted EU guidance.[7] Even though the study did not examine the same sub-therapeutic low dose as in the fixed combination, this requirement is not stipulated in the draft guideline expected to be adopted in 2010 (CPMP/EWP/238/95/95 Rev.3).

2. Reduction of (dose-dependent) adverse drug reactions by the low dose fixed combination as compared to the components in the lowest approved dosages.

In addition comparable or better BP reductions were observed in the moderate to severe subsets combined with a significantly lower rate of oedema than with high-dose amlodipine (A10). According to the TGA-adopted EU guidance trials should demonstrate a reduction of (dose dependent) adverse drug reactions by the low dose fixed combination as compared to the components in the lowest approved dosages.[7] The blood pressure lowering effect of the low dose fixed combination should be similar, that is, at least not inferior than those of the lowest approved dosage of each component, and there should be a trend towards better safety and response rate regarding the low-dose fixed combination as compared to each component administered at the lowest approved dosage.

Trial 1235.1 did demonstrate a trend towards improved safety with the low dose combinations as shown by the lower rates of oedema.

3. Trend towards better response rate

Initial therapy is also supported by the higher likelihood of achieving BP control with combination therapy. The results of trial 1235.1 support a usual starting dose of T40/A5 once daily. For patients requiring larger reduction of BP (patients with more severe hypertension or those requiring lower BP control targets such as diabetic patients with hypertension) a starting dose of T80/A5 may be used. The dosage can be increased after at least 2 weeks of therapy to a maximum of T80/A10 once daily as needed to control BP.

According to the TGA-adopted EU guidance, trials should demonstrate a trend towards better response rate regarding the low-dose fixed combination as compared to each component administered at the lowest approved dosage.[7] This was shown in study 1235.1.

The recommended starting dose strength should be T40/A5 once daily with the option for up-titration to a maximal dose of T80/A10 once daily. In patients with more severe hypertension who require larger reductions within a shorter period of time, a starting dose of T80/A5 may be used. This is supported by the larger BP reduction achieved with T80+A5 versus T40+A5 in this subset of patients (a 2.0 mmHg difference in trough DBP, a 2.6 mmHg difference in the ABPM substudy).

4. Improved compliance

In the EMEA draft guidelines CPMP/EWP/238/95/95 Rev.3 it is stated that a simplification of the therapy which improves patient compliance may justify the use of a fixed combination. A reference was provided to support that FDCs do improve compliance.[11] In the meta-analysis a MEDLINE search of fixed-dose combination compliance studies was performed and 68 studies were identified, 9 of which fulfilled inclusion criteria. A subgroup analysis of the 4 studies on hypertension showed that fixed-doe combination (pooled RR 0.76; 95% CI, 0.71-0.81; P<0.0001) decreased the risk of medication non-compliance by 24% compared with the free-drug combination regimen. The authors concluded that "Fixed-dose combination decreases the risk of medication non-compliance and should be considered in patients with chronic conditions like hypertension for improving medication compliance which can translate into better clinical outcomes."

Indication for first-line therapy in a broad patient population

The data presented from trial 1235.1 support the indication for first line use for the following reasons**:**

1) The 2003 European Society of Hypertension/European Society of Cardiology (ESH/ESC) Guidelines acknowledge that 20-30% of patients will require more than one drug to control blood pressure.

2) In the TGA-adopted EU guidance first-line therapy can be justified if[7]:

- It is demonstrated that each substance (component) has a documented contribution within the (fixed) combination. This was shown in study 1235.1
- There is a reduction of (dose-dependent) adverse drug reactions with the low dose fixed combination. This was shown in trial 1235.1.

3) In the EMEA draft guidelines CPMP/EWP/238/95/95 Rev.3 it is stated that in special instances a simplification of the therapy which improves patient compliance may justify the use of a fixed combination. The draft guidelines state that initial therapy with 2 drugs should be considered when blood pressure is more than 20/10 mmHg above goal. The 2003

[11] Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med 2007; 120:713-719.

European Society of Hypertension/European Society of Cardiology (ESH/ESC) Guideline recommends that drug therapy should be started gradually either with monotherapy or with a "low dose" combination, irrespectively of initial blood pressure levels. There is no recommendation on special patient groups to be considered for a first line combination therapy. These guidelines therefore acknowledge that combination therapy may be appropriate for a broad population of patients with hypertension.

Long term therapy

The overall mean reduction of SBP/DBP between the final visit in trial 1235.7 and baseline in trial 1235.5 was 16.6/13.0 mmHg. Most of this reduction (11.6/8.5 mmHg) in non-responders to A5 occurred during the 8 weeks of double-blind treatment in trial 1235.5, with an additional reduction during the first 14 weeks of open-label treatment in trial 1235.7. The reduction in BP was maintained from Week 14 onwards.

Results from trial 1235.8 in non-responders to A10 supported those from trial 1235.7.

The overall mean reduction of SBP/DBP between the final visit in trial 1235.8 and baseline in trial 1235.6 was 14.7/12.6 mmHg. The majority of this reduction (9.8/8.2 mmHg) occurred during the 8 weeks of double-blind treatment in trial 1235.6, with an additional reduction during the first 14 weeks of open-label treatment in trial 1235.8. The reduction in BP was maintained from Week 14 onwards.

Analyses of the secondary categorical BP endpoints (DBP and SBP control, DBP and SBP response, BP categories) supported the analyses of changes in DBP and SBP. All of these variables showed further improvement during open-label treatment in trials 1235.7 and 1235.8.In both trials, long-term treatment with the T/A FDCs proved to be efficacious with or without additional antihypertensive therapy.

Overall, the evaluator considered that the data submitted for evaluation are sufficient to support efficacy of the telmisartan/amlodipine FDCs for use as initial therapy in hypertensive patients likely to need multiple drugs to achieve their blood pressure goals.

Safety

Introduction

Clinical safety data to support the safety assessment of the T/A FDC comprised data from:

- 2 pivotal, double-blind non-responder trials (trials 1235.5 and 1235.6) and
- 2 corresponding open-label follow-up trials (trials 1235.7 and 1235.8).
- 1 pivotal double-blind, factorial design trial to evaluate the combination of telmisartan and amlodipine compared to their respective monotherapy components and placebo as initial therapy in patients who are likely to need multiple drugs to achieve their BP goals (trial 1235.1).
- 5 pooled phase I trials in healthy subjects (bioequivalence trials 1235.3, 1235.4; food interaction trial 1235.12; drug interaction trials 1235.2, 502.126).

Patient exposure

Overall, 3505 patients with essential hypertension were included in the analysis of safety as they were treated with at least 1 dose of the FDC dose of telmisartan/amlodipine (T/A), the free combination of telmisartan plus amlodipine (T+A), telmisartan monotherapy, amlodipine monotherapy, or placebo in the randomised treatment periods of all phase III trials. In addition, 258 healthy subjects were treated in pooled phase I trials. The total number of patients included in the analyses of safety is presented by treatment, irrespective of dose, in Table 24.

Table 24: Patients included in the analyses of safety by treatment and trial, irrespective of dose

Trial	Placebo	Amlodipine	Telmisartan	T/A [a]	Total
Phase III					
1235.1	46	319	307	789	1461
1235.5	0	543	0	554	1097
1235.6	0	315	0	632	947
1235.7 [b]	0	0	0	976	976
1235.8 [b]	0	0	0	437	437
Phase I [c]	0	12	36	258	258

a Includes patients treated with a free combination of single entity tablets in trial 1235.1

b Patients in trials 1235.7 and 1235.8 had completed trials 1235.5 and 1235.6, respectively and are included in the totals for these trials. Patients on monotherapy in the double-blind trial were switched to T/A FDC in the follow-up trial. For the total numbers of patients treated with combination therapy during trials 1235.5, 1235.6, 1235.7, and 1235.8, see Table 1.2.1: 2.

c Subjects treated with treatment other than telmisartan + amlodipine represent subjects treated with amlodipine and telmisartan monotherapy in crossover studies; subjects are counted only once in the overall total number of subjects.

For the randomised treatment period of the non-responder trials 1235.5 and 1235.6, the planned duration of treatment was 8 weeks of randomised treatment in both trials. Accordingly, mean exposure to randomised treatment ranged from 55.8-57.6 days. The studies did not include any patients treated for > 1 year.

For the treatment period of trials 1235.7 and 1235.8, patients were grouped according to dose of trial medication they received; therefore patients could be counted in more than one dose group. Mean exposure to T/A FDC ranged from 91.8 days in the T40/A10 treatment group to 202.2 days in the T80/A10 treatment group. The total exposure to the T/A FDC ranged from 109.9-403.3 patient years. In study 1235.7, 294 patients (all T40/A5) were treated for at least 234 days. It was not stated if any patients were treated for > 1 year. In study 1235.8, 102 patients (T40/A10) and 1 patient (T80/A10) were treated for at least 238 days/34 weeks. It was not stated if any patients were treated for > 1 year.

All patients in the pooled combination and monotherapy groups and on placebo in trial 1235.1 and the pooled combination and monotherapy groups (T+A, T mono, and A mono) had similar mean exposure duration (range 55.5-55.7 days) and percentage of patients treated for >31 days (range 94.8-95.8%). The duration of exposure to T+A was 120.3 patient years. The study did not include any patients treated for > 1 year.

In the 5 pooled phase I trials, 258 healthy subjects were exposed to T+A for 849 patient-days; of these subjects, 36 were also exposed to telmisartan for 324 patient-days and 12 were also exposed to amlodipine for 108 patient-days.

Adverse events

Common adverse events

Trials 1235.5 and 1235.6

During the randomised treatment period of the pivotal double-blind non-responder trials 1235.5 and 1235.6, the most frequently reported AEs according to SOC were *General Disorders and Administration Site Conditions*. The higher incidence of AEs in this SOC was due to the high incidence of the most commonly reported PT, peripheral oedema. Peripheral oedema was generally more common in patients who were treated with amlodipine (A10: 16.2%; A5: 8.2%), with lower incidences reported for combination therapies that included

A10 (T80/A10: 8.5%; T40/A10: 6.7%) or A5 (T40/A5: 5.1%; T80/A5: 3.6%). There was only one case of generalised oedema (A5 group) and one case of oedema (A10 group) during the randomised treatment period. The incidences of common AEs other than peripheral oedema were comparable across all combination therapy and monotherapy groups. Back pain, dizziness, and headache were each reported by 2.2% of T80/A5 patients and headache was reported by 3.4% of A5 patients. All other AEs were reported by <2% of patients in any treatment group.

Trials 1235.7 and 1235.8

In the follow-up trials in which patients were administered the combination therapy of T/A for up to 34 weeks, according to SOC, *Infections and Infestations* were the most common AEs overall. Based on exposure adjusted frequencies, such events were more common in patients treated with T40/A5 (33.22/100 per year [PY]) and T80/A5 (36.09/100 PY) than in the T40/A10 (10.01/100 PY) and T80/A10 (17.32/100 PY) treatment groups. This difference in overall frequency was not a reflection of a high incidence of any particular PT but resulted from low incidences of many different PTs within this SOC, including most commonly in all patients, nasopharyngitis (2.8%), bronchitis (2.3%), upper respiratory tract infection (1.3%), and rhinitis (1.1%). There was no clinically significant difference in the incidence of peripheral oedema across treatment groups, which ranged from 9.92-10.10/100 PY for the T40/A5, T80/A5 and T40/A10 treatment groups and was slightly lower for the T80/A10 treatment group (6.93/100 PY). The incidence of common PTs other than peripheral oedema was generally comparable across all treatment groups. Back pain, dizziness, and hypercholesterolaemia were the only other PTs with an incidence >5/100 PY in at least 1 treatment group.

Trial 1235.1

In trial 1235.1, in which T+A was administered as initial antihypertensive therapy, the most frequently reported AEs in the pooled therapies in trial 1235.1 were *General Disorders and Administration Site Conditions*, with the highest incidence for the A mono group and lower incidences for pooled combination therapy and T mono groups (11.9% A mono, 8.5% pooled combination therapy, 4.2% of T mono groups). *Musculoskeletal and Connective Tissue Disorders* and *Nervous System Disorders* were each reported by ≥5% of patients in both pooled monotherapy groups and the incidences were comparable across all pooled groups.

The most common PTs for the pooled combination therapy group were peripheral oedema (4.8%), headache (4.7%), dizziness (3.0%), and back pain (2.2%), (Table 25). The incidence of the most common AEs was generally lower in the T mono group than in the pooled combination therapy or A mono groups. As expected and in line with the known safety profile of amlodipine, the incidence of peripheral oedema was higher for A mono (7.8%), not only compared with T mono (0.7%), but also compared with pooled combination therapy (4.8%).

Table 25: AEs reported by at least 1% in any pooled combination or monotherapy group in trial 1235.1 (treated set)

System organ class Preferred term	Number (%) of patients			
	T+A (T20+A2.5-T80+A10)	T mono (T20-T80)	A mono (A2.5-A10)	Placebo
Treated	789	307	319	46
Total with any AEs	299 (37.9)	113 (36.8)	115 (36.1)	18 (39.1)
Gastrointestinal disorders	34 (4.3)	19 (6.2)	14 (4.4)	4 (8.7)
Abdominal pain upper	4 (0.5)	3 (1.0)	0 (0.0)	1 (2.2)
Diarrhoea	6 (0.8)	6 (2.0)	4 (1.3)	1 (2.2)
Nausea	2 (0.3)	2 (0.7)	5 (1.6)	0 (0.0)
General disorders and administration site conditions	67 (8.5)	13 (4.2)	38 (11.9)	1 (2.2)
Chest pain	6 (0.8)	5 (1.6)	1 (0.3)	1 (2.2)
Fatigue	9 (1.1)	6 (2.0)	4 (1.3)	0 (0.0)
Oedema	9 (1.1)	0 (0.0)	3 (0.9)	0 (0.0)
Oedema peripheral	38 (4.8)	2 (0.7)	25 (7.8)	0 (0.0)
Infections and infestations	82 (10.4)	27 (8.8)	28 (8.8)	6 (13.0)
Influenza	14 (1.8)	0 (0.0)	4 (1.3)	0 (0.0)
Nasopharyngitis	9 (1.1)	6 (2.0)	2 (0.6)	2 (4.3)
Pharyngitis	3 (0.4)	3 (1.0)	1 (0.3)	1 (2.2)
Sinusitis	9 (1.1)	2 (0.7)	3 (0.9)	2 (4.3)
Upper respiratory tract infection	11 (1.4)	6 (2.0)	6 (1.9)	0 (0.0)
Musculoskeletal and connective tissue disorders	48 (6.1)	17 (5.5)	19 (6.0)	3 (6.5)
Arthralgia	7 (0.9)	3 (1.0)	2 (0.6)	1 (2.2)
Back pain	17 (2.2)	3 (1.0)	7 (2.2)	0 (0.0)
Nervous system disorders	70 (8.9)	30 (9.8)	27 (8.5)	6 (13.0)
Dizziness	24 (3.0)	4 (1.3)	4 (1.3)	1 (2.2)
Headache	37 (4.7)	18 (5.9)	19 (6.0)	5 (10.9)
Psychiatric disorders	9 (1.1)	10 (3.3)	1 (0.3)	1 (2.2)
Anxiety	1 (0.1)	4 (1.3)	0 (0.0)	0 (0.0)
Insomnia	4 (0.5)	3 (1.0)	1 (0.3)	1 (2.2)
Vascular disorders	12 (1.5)	3 (1.0)	5 (1.6)	0 (0.0)
Hypertension	1 (0.1)	2 (0.7)	4 (1.3)	0 (0.0)

Oedema peripheral

For the total study population, oedema peripheral was reported in 65 (4.4%) patients with the following occurrences in each of the treatment groupings:

- Placebo: 0 (0.0%)
- Telmisartan monotherapy: 2 (0.7%)
- Amlodipine monotherapy: 25 (7.8%)
- Combination: 38 (4.8%).

The increased incidence of oedema peripheral in amlodipine monotherapy patients was most prevalent in those patients randomised to A10. No dose dependent effect was seen in Telmisartan monotherapy treated patients. Table 26 displays the frequency of patients with oedema peripheral.

Table 26: Frequency [N (%)] of patients with oedema peripheral by treatment group (Treated set),

	A0	A2.5	A5	A10
T0	0 (0.0)	1 (2.0)	1 (0.7)	23 (17.8)
T20	0 (0.0)	1 (2.3)	2 (4.3)	5 (11.4)
T40	1 (0.8)	0 (0.0)	2 (1.4)	8 (6.2)
T80	1 (0.7)	1 (2.1)	3 (2.1)	16 (11.3)

Pooled Phase I trials

The most common AE among subjects in the pooled Phase I trials was headache, which was experienced by 104/258 (40.3%) subjects in the T+A group, by 5/36 (13.9%) subjects in the telmisartan group and by 7/12 (58.3%) subjects in the amlodipine group. Other common AEs in the T+A group include nasopharyngitis (18 subjects, 7.0%), nausea (15 subjects, 5.8%), fatigue (8 subjects, 3.1%), dizziness (7 subjects, 2.7%), and vomiting (5 subjects, 1.9%), while diarrhoea, dyspepsia and pharyngolaryngeal pain was experienced by 3 subjects (1.2%). Two subjects (5.6%) in the telmisartan group experienced thrombophlebitis (compared to 1 subject, 0.4% in the T/A group and no subjects in the amlodipine group). Other AEs experienced by ≥1% of subjects in the telmisartan group include back pain, fatigue, haematoma, road traffic accident, tendonitis, and wound, each experienced by one subject (2.8%). AEs experienced by ≥1% of subjects in the amlodipine group included dizziness, conjunctivitis, and flatulence, each experienced by 1 subject (8.3%). The incidence of dizziness, which is an AE potentially related to BP lowering, was comparable in the T+A and amlodipine groups.

Drug-related AEs

Trials 1235.5 and 1235.6

During the randomised treatment period of the pivotal double-blind nonresponder trials 1235.5 and 1235.6, drug-related AEs were less frequent for patients on combination therapy than on amlodipine. The most frequently reported drug-related AEs according to SOC were *General Disorders and Administration Site Conditions* and the frequency of AEs in this SOC was higher for patients on amlodipine than on combination therapy (except T80/A10, which was comparable with the A5 monotherapy group) and higher on A10 monotherapy than on A5 monotherapy. The higher incidence of AEs in this SOC was due to the high incidence of peripheral oedema, which was the most common drug-related AE in all treatment groups. It was more common in patients treated with A10 as monotherapy (13.9%) or A5 (7.1%) than for patients on telmisartan in combination with A10 (T40/A10: 5.4%; T80/A10: 6.9%). Likewise it was more common for patients A5 (7.1%) than for those on telmisartan in combination with A5 (T40/A5: 3.2%; T80/A5: 2.9%). With the exception of peripheral oedema, the incidence of drug-related AEs was low and comparable across all monotherapy and combination therapy groups. There were no cases of drug-related syncope or orthostatic hypotension in any treatment group; there was one case of drug related hypotension (T40/A10 treatment group).

Trials 1235.7 and 1235.8

In the follow-up trials the incidence of drug related AEs was similar across all doses of FDC. The most frequently reported drug related AEs according to SOC were *General Disorders and Administration Site Conditions*. The only drug related AEs reported by ≥1% of patients in any dose group were peripheral oedema and dizziness. There was no clinically meaningful difference in the incidence of peripheral oedema across dose groups. The incidence of

dizziness was higher in the T80/A5 (2.89/100 PY) and T80/A10 (2.89/100 PY) treatment groups than in the T40/A5 (0.25/100 PY) and T40/A10 (0/100 PY) treatment groups. One patient in the T40/A5 treatment group reported drug related hypotension (0.50/100 PY); 2 patients reported drug-related orthostatic hypotension (overall incidence 0.22/100 PY across all doses of FDC); both patients were in the T40/A5 treatment group (0.50/100 PY).

Trial 1235.1

In trial 1235.1, pooled telmisartan monotherapy patients had the lowest incidence of drug related AEs, while the highest incidence was reported in the pooled combination therapy patients. The most frequently reported drug-related AEs for the pooled combination therapy group, with an incidence of ≥1%, were peripheral oedema, dizziness and headache; however, the incidences for dizziness and headache were lower than with placebo. There were no cases of drug related orthostatic hypotension or syncope during the initial treatment period.

Overall, 167 (11.4%) patients experienced an AE designated by the investigator to be related to study drug. The lowest percentage of drug-related AEs were reported in patients assigned to telmisartan monotherapy: 20 (6.5%) patients and was similar among other treatment groupings: placebo: 6 (13.0%), amlodipine monotherapy: 39 (12.2%) and combination: 102 (12.9%) patients.

Pooled Phase I trials

Study drug-related AEs were experienced most frequently in the *Nervous System Disorders* SOC, with headache being the most frequently reported drug-related AE. Drug related headache was reported in 24.4% (63/258) of subjects receiving T+A, and in 58.3% (7/12) of subjects receiving amlodipine. None of the subjects receiving telmisartan reported any drug-related AEs.

Serious adverse events and deaths

Deaths

There were four deaths reported across all clinical trials: one patient during the run-in period of the pivotal double-blind non-responder trial 1235.5 (on A5); one patient during the randomised treatment period of trial 1235.6 (on T40/A10); one patient in the open-label follow-up trial 1235.8 (on T80/A10); one patient in the pivotal double-blind initial therapy trial 1235.1 (on T80). None of the deaths were considered to be drug related. The fatal AEs were cerebrovascular accident, ruptured cerebral aneurysm, aortic dissection, and choking.

Serious adverse events (SAEs)

Trials 1235.5 and 1235.6

During the randomised treatment period of trial 1235.5, six patients had SAEs (A5: 2 patients, A10: 1 patient, T40/A5: 2 patients, T80/A5: 1 patient). No SAEs were fatal or immediately life ~~threatening,~~threatening and none were considered drug related by the investigator. All six patients completed the study without discontinuing trial medication.

During the randomised treatment period of trial 1235.6, four patients experienced SAEs (A10: 1 patient; T40/A10: 3 patients). One patient died (ruptured cerebral aneurysm); the other three patients had SAEs but recovered by the end of the study. None of the SAEs were considered drug-related and all required hospitalisation. The three non-fatal SAEs were local swelling (patient continued randomised treatment), cardiac failure (patient discontinued) and bronchitis (patient discontinued).

Trial 1235.1

Eight patients in trial 1235.1 reported treatment-emergent SAEs: 5 (0.6%) of 789 in the pooled combination therapy group, 1 (0.3%) of 307 in the T mono group, and 2 (0.6%) of 319 in the A mono group. SAEs with an onset prior to treatment (off treatment) were reported for 3 additional patients. The only SAE considered drug-related was chest pain in a patient receiving T80+A2.5. Two cases of pregnancy occurred under randomised treatment in trial 1235.1. These cases led to therapeutic abortion in one case and premature labour in the other case.

Laboratory findings

Trials 1235.5 and 1235.6

For trials 1235.5 and 1235.6, patients were required to be fasting for 8 to 10 hours before blood samples were collected. At baseline, patients had been treated with amlodipine (A5 for 6 weeks in trials 1235.5 or A5 for 2 weeks followed by A10 for 6 weeks in trials 1235.6). Thus, the analyses of clinical laboratory parameters investigated the changes that occurred after the switch from the run-in treatment to the randomised treatment.

There was a small and comparable decrease in mean haemoglobin levels for patients on all doses of the T/A FDC (mean change in haemoglobin from baseline to the end of the trial ranged from -0.3 to -0.7 g/dL for the FDC); changes in haemoglobin were slightly lower in amlodipine groups (-0.1 g/dL for each of the amlodipine groups).

The mean changes from baseline to the end of the trial for liver enzymes (aspartate transaminase [AST], alanine transaminase [ALT] or alkaline phosphatase levels) for all doses of FDC treatment and for amlodipine were slight, ranging from +4 to -3 U/L. The difference in the mean change for creatine phosphokinase (CPK) of +15 U/L for T40/A5 compared with a mean change of -3 to +3 U/L for other doses of the FDC was not considered clinically relevant considering the large sds for this parameter. Mean changes in creatinine from baseline to the end of the trial were negligible and comparable for combination therapy and monotherapy treatment groups. There was a small and comparable increase in mean uric acid values from baseline to the end of the trial for patients on all doses of the T/A FDC (range +0.2 to +0.4 mg/dL for the FDC) compared with little or no mean change for amlodipine monotherapies (+0.1 to -0.0 mg/dL).

Trials 1235.7 and 1235.8

Overall, mean changes in laboratory values from baseline to the end of the trial were small and not clinically meaningful, and were generally always <10% of baseline values.

Trial 1235.1

In trial 1235.1, mean changes in laboratory values from baseline to the end of the trial were small (<10% of baseline values) and similar across all pooled combination and monotherapy groups for all laboratory tests, with occasional larger changes in the placebo group. Mean changes in laboratory values consistent with laboratory findings described for telmisartan (small decreases in haemoglobin and small increases in liver function tests [LFTs]) were observed at similar magnitude in the pooled combination therapy group and the T mono group. No mean changes in creatinine were observed.

Safety in special populations

Intrinsic factors

For all double-blind and open-label follow-up trials, AE and laboratory tabulations were produced by the subgroups of sex, age, race, BMI, diabetes status, and renal function. For all

trials there was no consistent or clinically meaningful pattern of differences in the safety profile across subgroups of intrinsic factors for the T/A FDC. The overall incidences of most AEs were low in all treatment groups and generally there were no marked differences between subgroups.

Safety related to drug-drug interactions and other interactions

Pharmacokinetic interaction trials 1235.2 and 502.126, and the pivotal factorial design trial1235.1 demonstrated the absence of any pharmacokinetic or pharmacodynamic interaction between telmisartan and amlodipine.

The BP lowering effect of T/A FDC may be increased with concomitant use of other antihypertensive medicinal products. In addition, medicinal products with BP-lowering effects (for example, barbiturates, narcotics, antidepressants, baclofen, amifostine and alcohol) may potentiate the hypotensive effects of antihypertensive agents including T/A FDC. Corticosteroid containing medicinal products for systemic use may reduce the antihypertensive effect of T/A FDC.

Discontinuation due to adverse events

Trials 1235.5 and 1235.6

For the pooled data set from trials 1235.5 and 1235.6, during the randomised treatment period, AEs leading to discontinuation were most frequently reported by patients treated with A10 either as monotherapy (4.7%) or in combination with T40 (T40/A10: 2.9%). For all other treatment groups the incidence was no more than 2% of patients (1.1 to 1.9%), and was highest for the A5 monotherapy group. Although not permitted according to the protocol, during the randomised treatment period, dose reductions were reported for one patient in trial 1235.5 (A10 group, peripheral oedema) and for two patients in trial 1235.6 (T40/A10 seasonal allergy; T80/A10: peripheral oedema). The most common AE leading to discontinuation was peripheral oedema and the incidence was higher in the A10 group (3.6%) than in all other treatment groups (range: 0.0-0.7%). No other AEs leading to discontinuation were reported by ≥1% of patients in any treatment group. Dizziness was reported by three (0.5%) A10 patients and face oedema by two (0.3%) of the A10 patients. All other AEs leading to discontinuation were each reported by only one patient.

Trial 1235.1

AEs leading to treatment discontinuation in trial 1235.1 were reported for comparable percentages of patients in the pooled combination and monotherapy groups (2.0% to 2.5%), with a higher frequency in the placebo group (4.3%). The most frequent AEs overall leading to discontinuation in the pooled combination therapy group were peripheral oedema (0.5%), dizziness (0.4%), and hypotension (0.4%). No AE leading to discontinuation was reported for >0.9% of patients in any of the pooled combination and monotherapy groups. Incidences in the pooled combination therapy group were comparable to or lower than those in one or both pooled monotherapy groups for all PTs except hypotension, which was reported only in the pooled combination therapy group.

Evaluator's overall conclusions on clinical safety

In the clinical trials combination therapy showed a favourable safety profile, with lower oedema rates than amlodipine monotherapies, especially when comparing amlodipine full-dose monotherapy with amlodipine low-dose combinations, which showed at least comparable or better efficacy. AEs potentially related to BP lowering (for example, hypotension, orthostatic hypotension, syncope) were rare throughout the double-blind

treatment period of trial 1235.1, including the initial 2 weeks of first-line combination therapy. There were no serious cases. Almost all of the events reported in the trials were of mild or moderate intensity, and the majority of patients continued treatment and recovered without requiring therapy. No unexpected long-term side effects were observed when T/A FDC was administered to patients with adequate DBP control on amlodipine monotherapy at the end of the pivotal nonresponder trials. These patients not requiring combination therapy tolerated the T/A FDC well during 6 months of long-term treatment in the follow-up trials.

No unexpected changes in laboratory values, physical examination, pulse rate or ECG readings were reported. Orthostatic changes were infrequently reported as an adverse event. No unusual safety concerns were reported in the trials.

Clinical Summary and Conclusions

Clinical aspects

Clinical pharmacology

A single clinical pharmacology trial of the T/A FDC was undertaken; trial 1235.2. It was an open-label, randomised, 2-way crossover study in 38 healthy subjects to compare the steady state pharmacokinetics of the highest telmisartan dose (80 mg) alone and with amlodipine (10 mg). The trial showed that amlodipine did not alter the pharmacokinetics of telmisartan at steady state.

An earlier trial (502.126) demonstrated that telmisartan (120 mg) had no effect on the steady state pharmacokinetics of amlodipine (10 mg). In conclusion, the two interaction studies demonstrated that there is no significant drug-drug interaction between the 2 substances.

In this application the sponsor provided data to support the use of 4 telmisartan and amlodipine FDC dose strengths (T40/A5, T40/A10, T80/A5 and T80/A10) for the treatment of hypertension, both as add-on therapy in patients not adequately controlled on antihypertensive amlodipine therapy, and as initial therapy in patients likely to need multiple drugs to achieve their BP goals.

Efficacy

Add-on therapy

Trials 1235.5 and 1235.6 were the pivotal trials investigating the efficacy of the T/A FDCs in hypertensive patients who did not respond adequately to 6 weeks of A5 or A10 monotherapy. In trial 1235.5, T80/A5 and T40/A5 were statistically superior not only to continuing treatment with A5 but also to increasing the amlodipine dose from 5 mg to the maximum registered dose of 10 mg. In trial 1235.6, T80/A10 and T40/A10 were superior to continuing treatment with A10. The combination treatments also resulted in significantly larger reductions of trough sSBP compared to amlodipine monotherapy. These observed reductions in DBP obtained in amlodipine non-responders are considered clinically relevant as described in recent publications and guidelines. Analyses of mean BP changes over time showed that the most of the reduction in DBP and SBP was already apparent within 4 weeks of treatment.

Analyses of the secondary categorical BP endpoints (DBP and SBP control, DBP and SBP response, BP categories) and probabilities of achieving BP control depending on baseline BP supported the analyses of changes in DBP and SBP. For all endpoints the T80/A5 and T40/A5 groups showed better efficacy than the A5 group; the same was true for the T80/A10 and T40/A10 groups compared to the A10 group. T80/A5 was consistently more efficacious

than A10 and T40/A5 displayed at least numerically better BP effects than A10 for most efficacy variables.

In trial 1235.5 (A5 non-responders), the incidence of oedema for the pooled T/A groups was significantly lower (both statistically and clinically) than when amlodipine was up-titrated to A10 demonstrating the superiority of the combination treatment for both BP reductions and less oedema. In trial 1235.6 (A10 non-responders), the rate of oedema was generally comparable across the treatment groups but fewer patients on combination therapy discontinued due to oedema than on A10 monotherapy.

Results of subgroup analyses by age (<65≥65 years), sex (male/female), BMI category (<30/≥30 kg/m²), did not reveal any notable differences in efficacy.

These efficacy results adequately support the use of T/A combination therapy at dose strengths of T40/A5, T40/A10, T80/A5 and T80/A10 once daily to treat hypertension in patients who do not respond adequately to treatment with amlodipine monotherapy at either of the daily recommended doses of 5 or 10 mg.

Replacement therapy

Trials 1235.5, 1235.6, 1235.7, and 1235.8 were performed with the T/A FDC tablets intended for marketing, whereas trial 1235.1 was performed with free combinations of the marketed telmisartan and amlodipine tablets.

Trial 1235.2 investigated the steady-state pharmacokinetics of the highest telmisartan dose (80 mg) alone and in combination with amlodipine 10 mg. The results of this study showed that amlodipine did not alter the pharmacokinetics of telmisartan at steady state. A study conducted in the telmisartan (Micardis) monotherapy development program (trial 502.126) had already demonstrated that telmisartan had no effect on the steady-state pharmacokinetics of amlodipine.

Trials 1235.3 and 1235.4 examined the bioequivalence of the T40/A5 FDC (lowest dose strength) and the T80/A10 FDC (highest dose strength), respectively. In both studies, the FDC was found to be bioequivalent to the individual marketed tablets, when administered together.

Based on these results, patients receiving amlodipine and telmisartan from separate tablets can instead receive T/A FDC tablets containing the same component doses. This substitution reduces the number of tablets a patient has to take, which potentially enhances adherence to therapy, that is, improves compliance.

Initial therapy

Trial 1235.1 was performed in patients with DBP at baseline≥95 m mHg and ≤119 mmHg, of whom 79% (1129/1423) were moderate to severe hypertensives. The trial design and patient population was appropriate to assess first line use of the FDC. All 4 T+A key combination dose strengths showed superior efficacy compared to the respective monotherapies in the FAS after 8 weeks. The majority of the antihypertensive effect was attained within 2 weeks and close to the maximum observed antihypertensive effect that was observed within 4 weeks. The 4 key T+A combination treatment groups also attained greater BP reductions at 2 weeks compared to the monotherapy groups. Increasing doses of each component of the FDC produced incremental BP changes from baseline. Consistent with these results, DBP control rates increased over time, and with dosage, and were consistently higher in combination treatment than in the respective monotherapies. In the T+A combination groups, greater rates

of control (SBP and DBP) were noted at 2 weeks compared to the monotherapy groups. For the measures of DBP control (sDBP <90 mmHg) and DBP response (sDBP <90 mmHg or reduction from baseline≥10 mmHg), the highest proportions of patients were observed in the T80+A10 treatment group and the highest proportion of patients who qualified at the end of trial for the hypertensive classes of 'BP optimal' (BP <120/80 mmHg) and 'BP normal'(BP <130/85 mmHg but not optimal) was also in the T80+A10 group.

Superiority of combination compared to monotherapy treatment was further supported by the probability analyses for achievement of BP control in dependence of baseline BP. Further analyses were performed in 2 subsets of patients with moderate to severe hypertension at baseline (DBP100 subset, Grade 2/3 subset), that is, in patients in whom, according to current guidelines, combination therapy should be considered as first choice. Similar results to those reported for the overall population were observed for these groups of patients. Significantly greater reductions in DBP and SBP were noted with combination therapy than with monotherapy. Additionally, more rapid reductions in BP with greater SBP and DBP control rates were noted for the T+A combination groups compared to the T and A monotherapy groups, providing further support for the use of initial therapy with T40/A5 and T80/A5 combinations.

As noted in the Conclusions on Efficacy (Initial therapy) the regulatory requirements if first line therapy is claimed for a fixed low dose combination were fulfilled to the satisfaction of the evaluator.

Long term therapy

The overall mean reduction of SBP/DBP between the final visit in trial 1235.7 and baseline in trial 1235.5 was 16.6/13.0 mmHg. Most of this reduction (11.6/8.5 mmHg) in non-responders to A5 occurred during the 8 weeks of double-blind treatment in trial 1235.5, with an additional reduction during the first 14 weeks of open-label treatment in trial 1235.7. The reduction in BP was maintained from Week 14 onwards.

Results from trial 1235.8 in nonresponders to A10 supported those from trial 1235.7. The overall mean reduction of SBP/DBP between the final visit in trial 1235.8 and baseline in trial 1235.6 was 14.7/12.6 mmHg. The majority of this reduction (9.8/8.2 mmHg) occurred during the 8 weeks of double-blind treatment in trial 1235.6, with an additional reduction during the first 14 weeks of open-label treatment in trial 1235.8. The reduction in BP was maintained from Week 14 onwards.

Analyses of the secondary categorical BP endpoints (DBP and SBP control, DBP and SBP response, BP categories) supported the analyses of changes in DBP and SBP.

Safety

In the clinical trials, combination therapy showed a favourable safety profile. There with lower rates of oedema than amlodipine monotherapy especially when comparing amlodipine monotherapy at full dose with amlodipine in the low dose combinations, while the latter showed at least comparable or better efficacy. Almost all of the events reported in the trials were of mild or moderate intensity. The majority of patients continued treatment and recovered without requiring any additional therapies. No unexpected long-term side effects were observed when T/A FDC was administered to patients with adequate DBP control on amlodipine monotherapy at the end of the pivotal non-responder trials. No unexpected changes in laboratory values, physical examination, pulse rate or ECG readings were reported. No unusual safety concerns were reported in the trials.

Benefit risk assessment

Benefits

In this application the sponsor provided data to support the use of 4 telmisartan and amlodipine FDC dose strengths (T40/A5, T40/A10, T80/A5 and T80/A10) for the treatment of hypertension, as add on therapy in patients not adequately controlled on antihypertensive amlodipine therapy, as replacement therapy and as initial therapy in patients likely to need multiple drugs to achieve their BP goals.

Add-on therapy

As discussed in the previous section (Add on therapy), the efficacy results from Trials 1235.5 and 1235.6 adequately support the use of T/A combination therapy at dose strengths of T40/A5, T40/A10, T80/A5 and T80/A10 once daily to treat hypertension in patients who do not respond adequately to treatment with amlodipine monotherapy at either of the daily recommended doses of 5 or 10 mg.

Replacement therapy

As discussed in the previous section (replacement therapy), based on the results from Trials 1235.2, 1235.3, and 1235.4, patients receiving amlodipine and telmisartan from separate tablets can instead receive T/A FDC tablets containing the same component doses. This substitution reduces the number of tablets a patient has to take, which potentially enhances adherence to therapy, that is, improves compliance.

Initial therapy

As noted in the Conclusions on Efficacy (Initial therapy) the results from Trial 1235.1 fulfilled the regulatory requirements if first line therapy is claimed for a fixed low-dose combination to the satisfaction of the evaluator.

A starting dose strength of T40/A5 once daily is recommended with the option for up-titration to a maximal dose of T80/A10 once daily. In patients with more severe hypertension who require larger reductions within a shorter period of time, a starting dose of T80/A5 may be used. This is supported by the larger BP reduction achieved with T80+A5 versus T40+A5 in this subset of patients (a 2.0 mmHg difference in trough DBP, and a 2.6 mmHg difference in the ABPM substudy).

Indication for first-line therapy in a broad patient population

As also noted in the Conclusions on Efficacy (Initial Therapy), the results from trial 1235.1 support the indication for first line use and the guidelines acknowledge that combination therapy may be appropriate for a broad population of patients with hypertension.

Long term therapy

As noted in the Conclusions on Efficacy (Long term therapy), in both Trials 1235.7 and 1235.8, long-term treatment with the T/A FDCs proved to be efficacious with or without additional antihypertensive therapy.

Risks

As noted in the previous section (Safety) the clinical trials combination therapy showed a favourable safety profile, with lower oedema rates than amlodipine monotherapies, especially when comparing amlodipine full-dose monotherapy with amlodipine low-dose combinations, which showed at least comparable or better efficacy. No unusual safety concerns were reported in the trials.

Balance

Hypertension is a common disease and a contributory factor to the development of cardiovascular and cerebrovascular disease, including stroke, myocardial infarction, heart failure, and kidney disease. Reducing BP has consistently been shown to reduce the risk of cardiovascular events and recent studies suggest that continued benefit can be gained by reducing BP to normotensive levels.

The T/A FDC is a combination product comprised of telmisartan and amlodipine supplied in telmisartan / amlodipine dosage strengths of 40/5 mg, 40/10 mg, 80/5 mg, and 80/10 mg. The proposed indication is for the treatment of essential hypertension as replacement therapy in patients already taking both monotherapies separately, as add-on therapy in patients whose BP is not adequately controlled with amlodipine, or as initial therapy in patients likely to need multiple drugs to achieve their BP goals.

In the pivotal trials 1235.5 and 1235.6 supporting use of the FDC as add-on therapy, administration of the T/A FDCs for 8 weeks to patients who had not responded to amlodipine (DBP >90 mmHg) resulted in statistically and clinically significantly higher reductions in mean DBP and SBP than amlodipine alone. The benefits of the combination therapy over amlodipine were already apparent within 4 weeks of treatment. The superiority of the TA/FDC over amlodipine in this setting was supported by results for other efficacy variables (BP control rates, BP response rates, and probabilities of achieving BP control). For all endpoints the T80/A5 and T40/A5 groups showed consistently better efficacy than the A5 group; the same was true for the T80/A10 and T40/A10 groups compared to the A10 group. T80/A5 was consistently more efficacious than A10 and even T40/A5 was superior to A10 in lowering DBP and SBP and was at least numerically better for most other efficacy variables. In addition, these efficacy results for the T40/A5 and T80/A4 FDCs were accompanied by significantly lower oedema rates compared to full-dose amlodipine monotherapy. The reductions in blood pressure and lower oedema rates were clinically meaningful.

Long-term open-label treatment with the T/A FDCs in the follow-up trials 1235.7 and 1235.8 resulted in further substantial, clinically relevant reductions in BP values and improvements in other BP variables. In most patients these benefits were obtained without the addition of other hypertensive agents.

In trial 1235.1, first-line combination therapy with telmisartan and amlodipine was investigated. Published TGA-adopted EU guidelines and more recent draft guidelines (CPMP/EWP/238/95/95 Rev.3) describe the need and the requirements for first-line combination therapy in the treatment of hypertension. In light of these guidelines the following aspects of the clinical data for the T/A FDC are relevant:

1. Trial 1235.1 results showed superior BP-lowering effect and demonstrated that each component has a contribution within the fixed combination.

2. Achievement of BP goal in a more timely fashion with combination therapy was shown in trial 1235.1.

3. There were lower rates of oedema and the safety profile of combination therapy was shown to be favourable in trial 1235.1.

Combination therapy showed a favourable safety profile, with lower oedema rates than amlodipine monotherapies, especially when comparing amlodipine full-dose monotherapy with amlodipine low-dose combinations. No new safety signal of concern emerged in the clinical trial program.

There may be a further benefit for the T/A FDC in terms of improved compliance. A reference was provided to support that FDCs do improve compliance.[11]

Conclusions

This evaluator considered that the overall benefit risk profile of the T/A FDC is positive. The achievement of the BP goal occurred in a more timely fashion with combination therapy. In addition, higher DBP control rates were observed at the earliest visit after 2 weeks but also at the end of the trials. Combination therapy, in general, resulted in consistently higher BP control rates after already 2 weeks of treatment and higher probabilities of achieving the BP goal compared to the respective monotherapies.

The data provided within this submission adequately demonstrate a favourable benefit/risk of the T/A FDC and support its use in patients with inadequate BP control on amlodipine, as replacement therapy, add-on therapy or as initial therapy for the treatment of hypertension.

The proposed indication is for the treatment of essential hypertension as replacement therapy in patients already taking both monotherapies separately, as add on therapy in patients whose BP is not adequately controlled with amlodipine, or as initial therapy in patients likely to need multiple drugs to achieve their BP goals. It was considered that the data submitted for evaluation is sufficient to support the proposed indication. It was therefore recommended that the application to register Twynsta should be approved.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a justification for a waiver for a Risk Management Plan (RMP). The request for a waiver was based on the following:

- The mono components of the FDC, telmisartan and amlodipine, are both active substances of medicinal products long established for the treatment of arterial hypertension.
- The FDC of telmisartan and amlodipine is indicated for the treatment of arterial hypertension, the mono components telmisartan and amlodipine have the same indication.
- The recommended dosages and posology of the FDC are comparable to the approved dosages and posologies of telmisartan and amlodipine.
- The FDC safety profile is comparable to the established safety profiles of telmisartan and amlodipine.
- No new safety signals have emerged from clinical trials exposing patients to a combination of telmisartan with amlodipine.
- Dedicated drug interactions studies (Trials 1235.2 and 502.126) have demonstrated the absence of interactions between telmisartan and amlodipine.

In 2009, the sponsor also submitted an application and a waiver for the RMP to the EMEA. The EMEA agreed that an EU RMP was not necessary. The Office of Medicines Safety Monitoring (OMSM) accepted the justifications for the waiver and no RMP was required for this evaluation.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

The sponsor submitted three bioavailability studies, two pharmacokinetic interaction studies, a justification for not generating bioavailability data using two of the tablet strengths (40/10 and 80/5 mg, the intermediate strengths) and a justification for using a US-registered amlodipine comparator in two of the bioavailability studies.

Approval of the submission was recommended with respect to chemistry and quality control. The pharmaceutical chemistry evaluator has not specifically recommended approval with respect to bioavailability but has made some comments. The most important of these is that food reduces the bioavailability of telmisartan, but not amlodipine. One of the bioavailability studies, Study 1235.12, demonstrated that food reduced AUC by 24% and C_{max} by 60%. The sponsor contends that this reduction in bioavailability with food should not cause a reduction in therapeutic efficacy. The pharmaceutical evaluator has referred the matter for clinical comment.

Otherwise from a bioavailability perspective, the proposed fixed-dose combination 40/5 mg, the lowest strength and the proposed fixed-dose combination 80/10 mg, the highest strength, were each shown to be bioequivalent to the corresponding doses of the co-administered monotherapies. The PK interaction studies demonstrated that after a single dose and at steady state, amlodipine does not affect the bioavailability of telmisartan. The justifications for not performing bioavailability studies on the intermediate strengths, 40/10 mg and 80/5 mg and for using an overseas reference amlodipine rather than the Australian-registered amlodipine were considered acceptable according to the pharmaceutical chemistry evaluator.

Nonclinical

The data package was assessed as appropriate for a fixed-dose combination of previously approved components. No significant novel or increased toxicities were noted for the telmisartan/amlodipine combination in a well conducted, GLP-compliant, 13 week bridging toxicology study in rats.

The nonclinical evaluator was of the opinion that the toxicities observed were well known, reversible “class’ effects and reflected target organ toxicities that can be monitored in clinical practice. The submitted PK data were not adequate to identify any potential pharmacokinetic interactions. Drug interaction studies were not performed by the sponsor. Published results indicate that amlodipine, which is metabolised by and also inhibits CYP3A4, can interact moderately with other drugs that are metabolised by CYP3A4. However, the nonclinical evaluator was of the opinion that the toxicity data did not indicate a cause for concern.

Both active substances have been approved and have been on the market for many years. There is extensive nonclinical and clinical information available (for both the individual components alone and in various dual combinations). Accordingly, the nonclinical evaluator was of the opinion that there are no novel clinical safety concerns raised by the nonclinical data and thus there are no nonclinical objections to the registration of Twynsta for the treatment of hypertension.

Clinical

Pharmacokinetics

Bioequivalence of 40 mg telmisartan/5 mg amlodipine fixed-dose combination compared with its monocomponents was demonstrated in Trial 1235.3 and bioequivalence of 80 mg telmisartan/10 mg amlodipine fixed-dose combination compared with its monocomponents was demonstrated in Trial 1235.4

Trial 1235.12 investigated the influence of food on the bioavailability of 80 mg telmisartan/10 mg amlodipine fixed-dose combination. For telmisartan, plasma concentration-time profiles after a high fat meal showed a markedly lower and slightly later peak compared to the fasted state. The high fat meal had a greater effect in reducing C_{max} and $AUC_{0-\infty}$ in the female subjects compared to the males. For amlodipine, there was no significant food effect. The Delegate requested the sponsor to justify why the clear reduction in bioavailability of telmisartan with food compared with the fasting state should not result in a corresponding reduction in therapeutic efficacy.

Trial 1235.2 investigated the pharmacokinetics of repeated oral doses of 80 mg telmisartan at steady state, alone and in combination with repeated oral doses of amlodipine at steady state and demonstrated that there was no clinically significant change observable in systemic exposure to telmisartan 80 mg on co-administration with amlodipine after dosing both medications to steady state.

Trial 502.126 investigated the pharmacokinetics of repeated oral doses of 10 mg amlodipine daily and of 10 mg of amlodipine and 120 mg telmisartan daily and demonstrated that telmisartan did not alter the pharmacokinetics of amlodipine.

Efficacy in Hypertension

Add-on studies

Study **1235.5**, one of the pivotal studies, was an 8-week, randomised, 4-arm, double-blind study to compare the efficacy and safety of the FDC telmisartan 40 mg/amlodipine 5 mg versus the FDC telmisartan 80 mg/amlodipine 5 mg versus amlodipine 5 mg monotherapy versus amlodipine 10 mg monotherapy in patients with hypertension who failed to respond adequately to treatment with amlodipine 5 mg monotherapy. The primary objectives were to demonstrate (a) that the FDCs telmisartan 40 mg/amlodipine 5 mg and telmisartan 80 mg/amlodipine 5 mg were superior to amlodipine 5 mg in reducing BP at 8 weeks, (b) that these same FDCs were not inferior to amlodipine 10 mg in reducing BP at 8 weeks and (c) that the incidence of oedema was lower for the pooled FDC treatment groups than for the amlodipine 10 mg group.

Study **1235.6**, another of the three pivotal studies, was an 8-week, randomised, 3-arm, double-blind study to compare the safety and efficacy of the FDC telmisartan 40 mg/amlodipine 10 mg versus the FDC telmisartan 80 mg /amlodipine 10 mg versus amlodipine 10 mg monotherapy in patients with hypertension who failed to respond adequately to treatment with amlodipine 10 mg monotherapy. The primary objective was to show that the FDC telmisartan 40 mg /amlodipine 10 mg and the FDC telmisartan 80 mg/amlodipine 10 mg were superior in reducing BP at 8 weeks compared with amlodipine 10 mg monotherapy.

Mean diastolic BP decreased in all treatment groups after 8 weeks of treatment with the double-blind trial medication. Decreases in the groups receiving combination therapy were consistently greater than those in the groups receiving amlodipine monotherapy (amlodipine 5 mg and amlodipine 10 mg in trial 1235.5, amlodipine 10 mg in trial 1235.6). In both trials, the highest reductions of diastolic BP were seen in the groups taking FDCs containing telmisartan 80 mg. The results for both trials are shown in Table 9.

While each of the FDCs were shown to have greater efficacy than the amlodipine monotherapies, there did not appear to be notable differences between the telmisartan 40 mg/amlodipine 5 mg and telmisartan 80 mg/amlodipine 5 mg FDCs in 1235.5 and between the telmisartan 40 mg/amlodipine 10 mg and telmisartan 80 mg/amlodipine 10 mg FDCs in 1235.6.

A similar pattern of changes was demonstrated for the change from baseline in systolic blood pressure. For both diastolic and systolic BP, larger decreases from baseline at week 4 were observed on the FDCs than on the amlodipine monotherapies. With regard to blood pressure control and response rates, the superiority of the telmisartan/amlodipine FDC over amlodipine monotherapy was confirmed. The FDC therapies were demonstrated to have a higher probability of achieving diastolic and systolic BP control than the amlodipine monotherapies.

In the pooled FDC groups of trial 1235.5, 4.4% of patients experienced oedema (5.2% in telmisartan 40 mg/amlodipine 5 mg group, 3.7% in telmisartan 80 mg/amlodipine 5 mg group), while in the amlodipine 10 mg group, the incidence was significantly higher (24.9%). The rate of peripheral oedema during the 6-week amlodipine 5 mg run-in treatment was 6.1% and was 8.2% for continued treatment with amlodipine 5 mg during the randomised phase. In contrast to trial 1235.5, similar oedema rates were reported for the pooled FDC groups, 7.3% (6.2% in T40/A10 & 8.4% in T80/A10) and for the amlodipine 10 mg group, 6.6%, in trial 1235.6. During run-in treatment with amlodipine 5 mg and amlodipine 10 mg, peripheral oedema was the most frequently reported AE (3.1% with amlodipine 5 mg and 16.65 with amlodipine 16.6%). Thus a substantial number of patients who did not tolerate amlodipine monotherapy discontinued during this run-in phase and only patients who tolerated amlodipine monotherapy were randomised. Given that co-administration of an ARB is postulated to mitigate the occurrence of oedema caused by a CCB, it is surprising to note the rates of oedema in the FDC groups in trial 1235.5 – 6.2% in T40/A10 and 8.4% in T80/A10. One would have expected these results to have been reversed. The sponsor was requested to comment on this finding.

Study **1235.1** was a randomised, double-blind, double-dummy, placebo-controlled, 4 x 4 factorial design trial to evaluate telmisartan 20, 40 and 80 mg tablets in combination with amlodipine 2.5, 5 and 10 mg capsules after 8 weeks of treatment in patients with Stage I or II hypertension, with an ambulatory blood pressure monitoring study. The primary efficacy variable was trough (24 hours post-dose) seated diastolic BP at the last visit during the treatment phase and the change from baseline in the trough seated diastolic BP was the primary endpoint.

Within trial 1235.1, analyses were also performed on two subsets of patients with hypertension that would potentially benefit most from initial therapy with two anti-hypertensive medications:

- Patients with diastolic BP $\geq$ 100 mmHg at baseline (DBP100) – prospective analysis
- Patients with diastolic BP $\geq$ 100 mmHg or SBP $\geq$ 160 mmHg at baseline (grades 2/3) – *post hoc* analysis.

Each combination therapy produced greater mean changes from baseline in trough seated diastolic BP than the respective monotherapies. At the end of trial 1235.1, mean diastolic BP changes ranged from -16.0 to -19.6 mmHg for the key combination treatment groups and from -13.0 to -16.5 mmHg for the monotherapy groups. The greatest change (-19.6 mmHg) was observed in the two combination groups, telmisartan 40 mg/amlodipine 10 mg and telmisartan 80 mg /amlodipine 10 mg. Observed and adjusted mean diastolic BP changes from baseline are shown in Tables 15 and 16.

Results of the analyses of the DBP100 and Grades 2/3 subsets were consistent with those presented for the FAS. The predicted mean change from baseline in the trough seated diastolic BP according to a response-surface model for the FAS is shown in Table 17 and graphically in Figure 1.

It is worthy of note that there appears to be no notable difference in the above predicted mean change from baseline between the three fixed dose combinations involving the highest dose of amlodipine, that is for the combinations telmisartan 20 mg/amlodipine 10 mg, telmisartan 40 mg/amlodipine 10 mg and telmisartan 80 mg/amlodipine 10 mg.

The key combination treatment groups produced greater mean reductions from baseline in systolic BP than the respective monotherapies for the FAS. Similar results were observed with the DBP100 and Grades 2/3. Administration of the key combination treatments led to earlier reductions in both diastolic and systolic BP than the monotherapies. Importantly, there is very little difference in these mean DBP and SBP changes from baseline between the amlodipine 10 mg monotherapy group and the two fixed dose combination groups, telmisartan 40 mg/amlodipine 5 mg and telmisartan 80 mg/amlodipine 5 mg.

In general, combination therapy was associated with higher rates of BP control and response than observed with the respective monotherapies. Response and control rates for the amlodipine 10 mg monotherapy group were similar to the rates for combination therapies that included amlodipine 5 mg while the combination therapies utilising amlodipine 10 mg resulted in the largest responses and control rates. For each of the BP response and control variables, results for the DBP100 and Grades 2/3 sub-sets were comparable to those observed for the FAS.

Results showed that combination therapy is associated with increased likelihoods of meeting the various BP goals, that is, DBP < 90 mmHg, DBP < 80 mmHg, SBP < 140 mmHg and SBP < 130 mmHg, in comparison with the respective monotherapies. These results would appear to have been generated as part of a *post hoc* analysis. The sponsor was requested to give a detailed commentary on how these analyses were generated. While agreeing that there is an increased likelihood of achievement of the various BP goals on combination therapy compared with the respective monotherapies, the Delegate made some comments. Firstly, it is quite striking how well amlodipine 10 mg monotherapy holds its own against the combination therapies of telmisartan 40 mg/amlodipine 10 mg and of telmisartan 80 mg/amlodipine 10 mg. Secondly, it is also quite striking to compare the likelihoods of achieving these various goals in the groups who received the latter two combination therapies, namely telmisartan 40 mg/amlodipine 10 mg and telmisartan 80 mg/amlodipine 10 mg. There is very little difference between these two groups. In fact for the two measures, DBP < 80 mmHg and SBP < 140 mmHg, the lower FDC strength, telmisartan 40 mg /amlodipine 10 mg outperforms the higher strength, telmisartan 80 mg /amlodipine 10 mg.

The Delegate noted that the diagrammatic counterparts of these tables are included in the US Full Prescribing Information for Twynsta (Figure 6).

Figure 6: Probability of Achieving Blood Pressure Control

The figures below provide estimates of the likelihood of achieving systolic and diastolic blood pressure control with TWYNSTA 80/10 mg tablets, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modeling. The estimated likelihood at the right tail of each curve is less reliable due to small numbers of subjects with high baseline blood pressures.

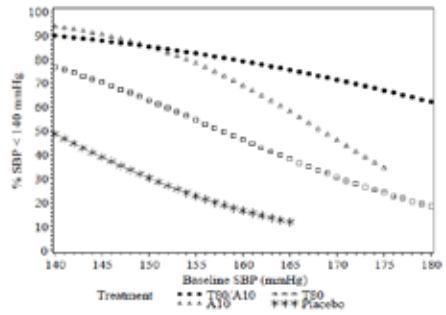


Figure 1a: Probability of Achieving Systolic Blood Pressure <140 mmHg at Week 8

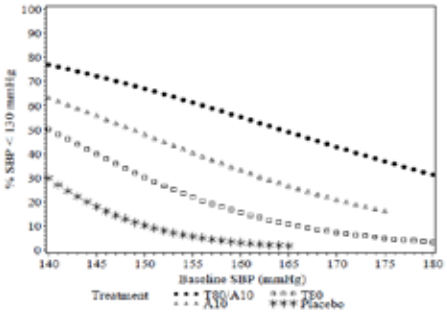


Figure 1b: Probability of Achieving Systolic Blood Pressure <130 mmHg at Week 8

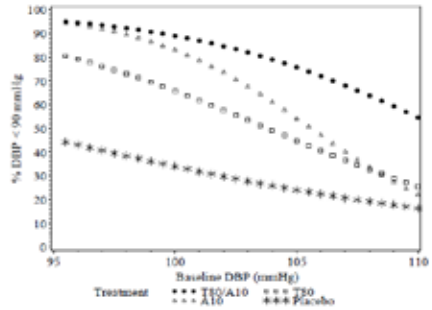


Figure 2a: Probability of Achieving Diastolic Blood Pressure <90 mmHg at Week 8

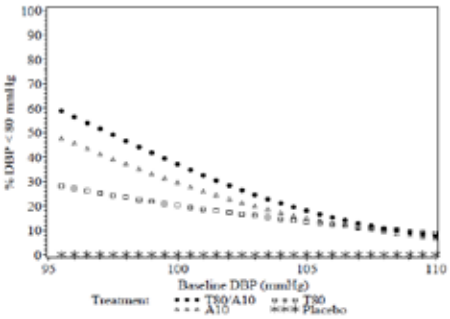


Figure 2b: Probability of Achieving Diastolic Blood Pressure <80 mmHg at Week 8

The figures above provide an approximation of the likelihood of reaching a targeted blood pressure goal at 8 weeks. For example, a patient with a baseline blood pressure of 160/110 mmHg has about a 16% likelihood of achieving a goal of <140 mmHg (systolic) and 16% likelihood of achieving <90 mmHg (diastolic) on placebo. The likelihood of achieving these same goals on telmisartan is about 46% (systolic) and 26% (diastolic). The likelihood of achieving these same goals on amlodipine is about 69% (systolic) and 22% (diastolic). These likelihoods rise to 79% for systolic and 55% for diastolic with TWYNSTA.

Each figure demonstrates that with increasing baseline BP, the likelihoods of achieving the stated goals steadily declines with all treatments. The Delegate expressed concerns about these results, not the least of which is that it is on the basis of these predictions that the indication for first-line treatment has been predicated. If these predictions are the result of a *post hoc* analysis, this is of great concern because such analyses can be biased and should not generally form part of the evidence base for an indication. This is all the more reinforced when one reads that the estimated likelihood at the right tail of each curve is less reliable due to small numbers of subjects with high baseline blood pressures. The next concern is that some of these graphs stop early. This is presumably because of small or perhaps non-existent numbers of patients with the corresponding high baseline BP levels. The sponsor was asked to clarify this issue. In each of the two figures at the left-hand side of Figure 6, there appears to be quite a drop in the likelihood of goal achievement by the amlodipine monotherapy 10 mg past the half-way point of the horizontal axis. The Delegate requested comment from the sponsor on whether the drivers for the graphical trends in these cases are low patient numbers. Finally, the figure at the bottom right hand corner, that for the goal of DBP < 80 mmHg, shows a clear convergence of the likelihoods of success of goal achievement for each of the three treatments, telmisartan 80 mg/amlodipine 10 mg, telmisartan 80 mg monotherapy and amlodipine 10 mg monotherapy, particularly from a baseline level of 100 mmHg. This perhaps in part a reflection of the fact that the particular goal in question, namely DBP < 80 mmHg, is possibly the most stringent of all the goals.

The reported incidence rates of oedema were 9.1% for patients who received amlodipine monotherapy, 0.7% for patients who received telmisartan monotherapy and 6.1% for the

patients who received telmisartan/amlodipine combination therapy. There were no reported cases of oedema in the placebo group. The majority of the cases of oedema occurred in the amlodipine 10 mg treatment groups and the highest incidence was found in patients who received the amlodipine 10 mg monotherapy (20.2%).

Patients who completed 8 weeks of randomised treatment in trials 1235.5 or 1235.6 were offered the option of receiving open-label treatment with the FDCs of telmisartan/amlodipine for up to 34 weeks in trials 1235.7 or 1235.8, respectively.

In Study **1235.7**, all patients initially received telmisartan 40 mg/amlodipine 5 mg. If BP goals were not achieved with telmisartan 40 mg/amlodipine 5 mg at weeks 4 or 8, the dose was to be up-titrated to telmisartan 80 mg/amlodipine 5 mg. There were 2 co-primary endpoints, the change from baseline in trough seated diastolic BP and the incidence of oedema during the double-blind phase. The overall mean reduction of trough seated diastolic BP between baseline of trial 1235.5 and the final visit of trial 1235.7 was 13.0 mmHg. The majority of this reduction, 8.5 mmHg, occurred during the 8 weeks of double-blind treatment in the preceding trial 1235.5. However, diastolic BP continued to decrease during the first 14 weeks of open-label treatment in trial 1235.7 and also the mean reduction in that parameter was maintained from week 14 onwards. These results are shown in Table 22.

The proportion of patients with oedema increased from 8.5% (82/965) at the end of trial 1235.5 to 13.7% (132/962) at the end of trial 1235.7. This is despite no increase in the dose of amlodipine (5 mg) at least for the first 8 weeks of the open-label extension. The sponsor was requested to comment.

In Study **1235.8**, all patients initially received telmisartan 40 mg/amlodipine 10 mg for a 4-week run-in period and were then randomised in a 3:2 ratio to treatment with telmisartan 80 mg/amlodipine 10 mg or telmisartan 40 mg /amlodipine 10 mg. After a further 4 weeks, that is at Week 8, patients randomised to telmisartan 40 mg /amlodipine 10 mg were up-titrated to telmisartan 80 mg /amlodipine 10 mg if they had not attained the diastolic BP goal of < 990 mmHg. The primary endpoint was the change from baseline in trough seated diastolic BP. The open-label follow-up trial 1235.8 was still ongoing at the time of the submission and results are based on an interim analysis (database lock point 9 April 2009). At this time point, 436 (48.8%) of the 894 patients who had completed trial 1235.6 had entered trial 1235.8. The overall mean reduction in trough seated diastolic BP between baseline of trial 1235.6 and the final visit of trial 1235.8 was 12.6 mmHg. The majority of this reduction (8.2 mmHg) occurred during the 8 weeks of double-blind treatment in the preceding trial 1235.6. Diastolic BP continued to decrease during the first 14 weeks of open-label treatment in trial 1235.8 and again the mean reduction in diastolic BP was maintained from Week 14 onwards. These results are shown in Table 23.

The proportion of patients with oedema increased from 10.3% (45/436) at the interim endpoint of trial 1235.6 to 15.4% (67/434). Again, this is despite an up-titration in the dose of telmisartan and amlodipine fixed at its maximum dose, 10 mg. The sponsor was requested to comment. The sponsor was also requested to provide, as part of its pre-ACPM response, the most up-to-date analysis of the results of the ongoing open-label study, 1235.8.

Summary of efficacy

Trials **1235.5** and **1235.6** were the pivotal trials investigating the efficacy of the telmisartan/amlodipine FDCs in reducing the mean trough seated diastolic BP in hypertensive patients who did not respond adequately to 6 weeks of amlodipine 5 mg or amlodipine 10 mg monotherapies, respectively. In trial 1235.5, telmisartan 80 mg /amlodipine 5 mg and telmisartan 40 mg/amlodipine 5 mg were statistically significantly superior both to

continuing treatment with amlodipine 5 mg monotherapy and to increasing the dose of the latter to the maximum of 10 mg. In trial 1235.6, telmisartan 80 mg/amlodipine 10 mg and telmisartan 40 mg /amlodipine 10 mg were statistically significantly superior to continuing treatment with amlodipine 10 mg. Comparable results were also achieved with the corresponding trough seated systolic BP parameter. Analyses of mean BP changes over time showed that most of the reduction in diastolic and systolic BP was apparent within 4 weeks of treatment. In general, analyses of the secondary categorical BP endpoints, e.g. diastolic and systolic BP control and response rates and the probabilities of achieving BP control *vis a vis* baseline BP supported the primary analyses.

In trial 1235.5 (amlodipine non-responders), the incidence of oedema for the pooled telmisartan/amlodipine FDC groups was statistically significantly lower than when amlodipine was up-titrated from 5 mg to 10 mg. In trial 1235.6 (amlodipine 10 mg non-responders), the rate of oedema was comparable across the treatment groups but fewer patients on combination therapy discontinued due to oedema than on amlodipine 10 mg monotherapy.

There was no clinical trial investigating the efficacy of the telmisartan/amlodipine FDCs in hypertensive patients who had not responded adequately to treatment with telmisartan monotherapy, that is, in telmisartan nonresponders.

Trial **1235.1**, all four key telmisartan/amlodipine combinations (40/5, 40/10, 80/5 and 80/10 mg) showed superior efficacy compared to the respective monotherapies. The 4 key telmisartan/amlodipine FDC groups also attained greater BP reductions at 2 weeks compared to the monotherapy groups. Generally, the superiority of combination compared to monotherapy treatment was further supported by the results for diastolic and systolic BP response and control rates, by the probability analyses for achievement of BP control according to baseline BP and by the analyses in the two relevant subsets of patients; the DBP100 and Grades 2/3 subsets.

Safety

Overall, 3505 patients with essential hypertension were included in the analysis of safety as they were treated with at least one dose of the fixed dose combination of telmisartan/amlodipine, the free combination of telmisartan + amlodipine, telmisartan monotherapy, amlodipine monotherapy or placebo in the randomised treatment periods of all the Phase III trials. Also, 258 healthy subjects were treated in the pooled Phase I trials.

During the randomised treatment period of the pivotal non-responder trials, 1235.5 and 1235.6, the most frequently reported AEs according to SOC were *General Disorders and Administration Site Conditions*, due to the high incidence of the most commonly reported preferred term, peripheral oedema. The latter was more common in patients treated with amlodipine only, that is amlodipine10 mg monotherapy (16.2%) and amlodipine 5 mg monotherapy (8.2%). There were lower incidences reported for the combination therapies that included amlodipine 10 mg (telmisartan 80 mg/amlodipine 10 mg [8.5%], telmisartan 40 mg/amlodipine 10 mg [6.7%]) or amlodipine 5 mg (telmisartan 80 mg/amlodipine 5 mg [3.6%], telmisartan 40 mg/amlodipine 5 mg [5.1%]). The incidences of common AEs other than peripheral oedema were comparable across all combination therapy and monotherapy groups. In trial 1235.1, in which the combination was administered as initial anti-hypertensive therapy, the most frequently reported AEs were in the SOC for *General Disorders and Administration Site Conditions*. The most common preferred terms for the pooled combination therapy group were peripheral oedema (4.8%), headache (4.7%), dizziness (3.0%) and back pain (2.2%). The incidence of the most common AEs was generally lower in the telmisartan monotherapy group than in the pooled combination therapy

or amlodipine monotherapy groups. As expected, the incidence of peripheral oedema was higher for amlodipine monotherapy (7.8%), not only compared with telmisartan monotherapy (0.7%) but also compared with pooled combination therapy (4.8%).

During the randomised treatment period of the pivotal non-responder trials, 1235.5 and 1235.6, drug-related AEs were less frequent for patients on combination therapy than on amlodipine. This was due to the high incidence of peripheral oedema which was the most common drug-related AE in all treatment groups. It was more common in patients treated with amlodipine 10 mg monotherapy (13.9%) or amlodipine 5 mg monotherapy (7.1%) than it was for patients on telmisartan in combination with amlodipine 10 mg (telmisartan 80 mg/amlodipine 10 mg [6.9%] and telmisartan 40 mg/amlodipine 10 mg [5.4%]) or in combination with amlodipine 5 mg (telmisartan 80 mg/amlodipine 5 mg [2.9%] and telmisartan 40 mg/amlodipine 5 mg [3.2%]). With the exception of peripheral oedema, the incidence of drug-related AEs was low and comparable across all monotherapy and combination therapy groups. There were no cases of drug-related syncope or orthostatic hypotension in any treatment group. There was one case of drug-related hypotension in the telmisartan 40 mg/amlodipine 10 mg combination group. In the open-label extension studies, 1235.7 and 1235.8, the only drug-related AEs reported by at least 1% of patients in any dose group were peripheral oedema and dizziness. There was no clinically meaningful difference in the incidence of peripheral oedema across dose groups. The incidence of dizziness was higher in the telmisartan 80 mg/amlodipine 5 mg (2.89/100 PY) and telmisartan 80 mg/amlodipine 10 mg (2.89/100 PY) treatment groups than in the telmisartan 40 mg/amlodipine 5 mg (0.25/100 PY) and telmisartan 40 mg/amlodipine 10 mg (0/100 PY) treatment groups. In the factorial design trial, 1235.1, the most frequently reported drug-related AEs for the pooled combination therapy group, with an incidence of at least 1%, were peripheral oedema, dizziness and headache. However, the incidences for dizziness and headache were lower than for placebo.

There were 4 deaths across all clinical trials (cerebrovascular accident, ruptured cerebral aneurysm, aortic dissection and choking). No death was considered drug-related. In the non-responder trials, 1235.5 and 1235.6, none of the SAEs was considered drug-related. In the factorial design trial, 1235.1, there was one SAE considered drug-related and that was chest pain in a patient receiving telmisartan 80mg/amlodipine 2.5mg.

Across all trials, the mean changes in laboratory values were small and generally similar across all pooled combination and monotherapy groups for all laboratory tests.

For all trials there was no consistent or clinically meaningful pattern of differences in the safety profiles across sub-groups of special populations with particular intrinsic factors.

In the two non-responder trials, the most common AE leading to discontinuation was peripheral oedema and the incidence was higher in the amlodipine 10 mg group (3.6%) than in all other treatment groups (range 0.0-0.7%). No other AEs leading to discontinuation were reported by at least 1% of patients in any treatment group. In the factorial design trial, AEs leading to discontinuation were reported for comparable percentages of patients in the pooled combination and monotherapy groups (2.0% to 2.5%), with a higher frequency in the placebo group (4.3%). The most frequent AEs overall leading to discontinuation in the pooled combination therapy group were peripheral oedema (0.5%), dizziness (0.4%) and hypotension (0.4%).

Summary of safety

In the clinical trials combination therapy showed a favourable safety profile, with lower oedema rates than amlodipine monotherapies. AEs potentially related to BP lowering were

rare throughout the double-blind treatment period of the factorial design study, 1235.1, including the initial two weeks of first-line combination therapy. There appear to have adequate numbers of patients included in the trials on the fixed dose combination with regard to the requirements for long term therapy. No unexpected changes in laboratory values, physical examination, pulse rate or ECG readings were reported.

Summary of clinical evaluator's recommendation

The clinical evaluator was of the opinion that the data adequately demonstrated a favourable benefit/risk balance of the telmisartan/amlodipine fixed dose combination to support its use in patients with inadequate BP control on amlodipine or telmisartan, its use as replacement therapy and its use as initial therapy for the treatment of hypertension.

The pivotal trials, 1235.5 and 1235.6, provided evidence to support the use of the fixed-dose combinations as add-on therapy, with the addition of the combinations resulting in statistically and clinically significantly greater reductions in mean diastolic and systolic blood pressure than amlodipine 5 mg and 10 mg alone. There was no add-on study in telmisartan nonresponders and the evaluator has stated, without qualification, that the efficacy data from the factorial study 1235.1 is sufficient proof of the add-on benefit of amlodipine in telmisartan nonresponders.

Long-term open-label treatment with the fixed-dose combinations in the trials 1235.7 and 1235.8 resulted in further reductions in BP.

With regard to first-line treatment, the clinical evaluator has considered the following results from the pivotal factorial trial 1235.1:

- The superior BP lowering effect of the combinations and the demonstration that each component of the combination has a contribution within that fixed dose combination;
- The achievement of BP goals in a more timely fashion with combination therapy, and
- The lower rates of oedema with the combination therapy and the favourable safety profile of the combination therapy.

The clinical evaluator also mentioned that there may be a further benefit for the telmisartan/amlodipine fixed dose combination in terms of improved compliance, citing a meta-analysis provided by the sponsor.

Risk Management Plan

The sponsor submitted a justification for a waiver of the requirement for a Risk Management Plan and this was accepted by the Office of Product Review during the application entry phase.

Risk-Benefit Analysis

Delegate Considerations

The most relevant EU guideline is the TGA-adopted EU guideline on the treatment of hypertension.[8] For the claim of second-line therapy, it is usually necessary to establish the following:

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

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

The guideline states that it is mandatory that at least one pivotal clinical study is performed in a population of patients whose blood pressure cannot be normalised with monotherapy of one of the components. Trials 1235.5 and 1235.6 were the pivotal trials investigating the efficacy of the telmisartan/amlodipine fixed-dose combinations in hypertensive patients who did not respond adequately to 6 weeks of amlodipine 5 mg monotherapy or amlodipine 10 mg monotherapy and so this particular requirement of the guideline has been met. The next part of the guideline states that it is necessary to demonstrate a statistically significant and clinically relevant additional blood pressure reduction of the combination in patients who did not respond adequately to standard therapeutic doses of either monotherapy. Such sentences as the latter can imply that add-on studies should be done for both situations, that is, in this case in both amlodipine non-responders and telmisartan non-responders. There were no trials in this submission of the telmisartan/amlodipine fixed-dose combinations in hypertensive patients who did not respond adequately to treatment with telmisartan monotherapy. If it is assumed that the guideline means a requirement for at least one add-on study, it has been satisfied. However, this does not prevent the Delegate from regarding the absence of an add-on study in telmisartan non-responders as a deficiency. Nor does the Delegate agree with the clinical evaluator that "*the factorial data from the efficacy studies are considered sufficient to support approval of the telmisartan/amlodipine fixed-dose combination in patients not adequately controlled on telmisartan monotherapy*". If the latter statement were to be accepted then no add-on studies of any sort need be done as all could be proven in the factorial study. However, the latter was a purely parallel study which did not assess efficacy in any non-responders.

For the purpose of a claim in second-line therapy, all studies were well designed and well conducted. Studies 1235.5 and 1235.6 demonstrated a statistically significant and clinically relevant additional blood pressure reduction of the combination in patients who did not respond adequately to standard therapeutic doses of amlodipine. Analyses of the secondary categorical BP endpoints, for example, diastolic and systolic blood pressure control and response rates, the latter specifically mentioned by the guideline, were also consistent with the primary endpoints achieved.

The sponsor has provided additional evidence of a supportive nature to substantiate a claim of maintenance of therapeutic effect of up to 34 weeks in the trials 1235.7 and 1235.8 which were the open-label extensions of the add-on studies, 1235.7 and 1235.8, respectively.

Also required for the purpose of a claim in second line therapy is a parallel group comparison of the combination with the individual components using the same therapeutic doses with demonstration of statistically significant superior efficacy of the combination and no additional safety concerns outweighing the additional benefits of the fixed combinations. The Delegate agreed that these elements have been established by means of the pivotal factorial study, 1235.1. There are reduced rates of peripheral oedema on the fixed-dose combinations as compared to amlodipine monotherapy.

For approval as second line therapy, the Delegate did not regard the absence of a study in telmisartan nonresponders as a serious deficiency. Taking into account the evidence from the three pivotal studies, the Delegate had no objections to a recommendation for use of the fixed dose combination as second line therapy. However, the Delegate sought specific comment from the ACPM on the absence of a study in telmisartan non-responders.

For the purpose of claiming efficacy as first line therapy, the above guideline is not so helpful. It addresses necessary (but not sufficient) conditions to be satisfied by any application in which first line therapy is claimed. There are two such conditions, firstly demonstration that each component has a documented contribution within the (fixed) combination using sub-therapeutic doses and secondly demonstration of a reduction of (dose-dependent) adverse drug reactions by the low dose fixed combination as compared to the components in the lowest approved dosages. There was testing of sub-therapeutic doses apart from placebo. In the pivotal factorial study, 1235.1, patients were randomised into a 4 x 4 factorial design treatment allocation. Apart from the groups of primary interest, there were, for the purposes of this submission, a number of groups employing "sub-therapeutic doses" which were 0 mg of either or both components, 2.5 mg amlodipine and 20 mg telmisartan. These were the telmisartan/amlodipine groups 0/0, 0/2.5, 20/0, 20/2.5. However, the latter dose is not proposed for registration; neither are the doses 20/5, 40/2.5. The Delegate agreed that each component has been shown to make a documented contribution within the fixed dose combination. There was also demonstration of a reduction in one dose dependent adverse drug reaction, that is, peripheral oedema. There was no evidence of a worse safety profile for the fixed dose combination.

However, critically, the guideline does not address what would constitute the sufficient rather than necessary conditions for the proof of a first-line claim. These would have to vary on a case by case basis and the Delegate raised particular points of concern regarding this application. There are also problems in how one applies such particular guidelines when one looks at the actual evidence to support the claim of initial or first-line treatment. The draft guideline on hypertension, CPMP/EWP/238/95 Rev.3, which was cited by the clinical evaluator, has not yet been adopted.

Firstly, there are no data which directly compares the clinical efficacy and safety of the product given as a first-line treatment with the clinical efficacy and safety of the product given in response to an add-on indication. The latter strategy which by and large is accepted as clinical best practice is the one of careful dose titration and/or add-on therapy. It is a strategy which allows the clinician to gauge the efficacy and safety at each step. Very importantly such a strategy allows one to isolate effects such as the degree of efficacy and particular adverse events, the causality of which can then be appropriately assigned. There is no evidence which demonstrates that there is any significant difference in clinical outcome between patients treated via either of the two strategies. In the pivotal factorial study, each combination therapy produced greater mean changes from baseline in diastolic and systolic BP. Higher control rates were apparent after 2 weeks of treatment for the four key combination groups (57% to 63%) compared to the respective monotherapies. Does such an outcome necessarily always represent a gain or benefit? In current clinical practice, having observed that response after 2-4 weeks may not be optimal, the clinician is able to weigh up carefully and rationally the need for either dose titration and/or add-on treatment. There has been no evaluation of the proposed first-line treatment with the combination against the measured approach of dose titration and/or add-on therapy. As well from 4 weeks on, there was little difference in the mean diastolic and systolic BP changes from baseline, particularly the diastolic, between the amlodipine 10 mg monotherapy group and the two fixed-dose combination groups, telmisartan 40 mg/amlodipine 5 mg and telmisartan 80 mg/amlodipine 5 mg. There was also no clinical outcome data on morbidity or mortality.

Secondly, there was only one study, the pivotal factorial study 1235.1, in which all patients randomized to the combination groups received the combination of telmisartan/amlodipine as the initial treatment without titration from monotherapy. This immediately gives rise to a question about the design of the study. There was no guard against treatment at an

unnecessarily high dose. Because of the lack of any dose-titration, there is an important flaw in the study design. The design may be appropriate for dosage confirmation but not to test fully first-line efficacy. If for example, a patient had been randomized to the telmisartan/amlodipine 80/5 mg group, there would have been still a reasonable chance that BP control would have been achieved with telmisartan/amlodipine 40/5 mg and even with amlodipine 5 mg monotherapy. For example, the diastolic BP control rate on amlodipine 5 mg was 52.6%. Thus all other things being equal, one could expect that 52.6% of the patients treated with telmisartan/amlodipine 80/5 mg, or any of the other combinations, would have also similarly responded to just the amlodipine 5 mg monotherapy. The same applies when one compares the results from the same table for the three groups, telmisartan/amlodipine 80/10 mg, telmisartan/amlodipine 40/10 mg and amlodipine 10 mg.

It is as if the pivotal study, 1235.1, has been presented as a paradigm of clinical practice but it is an incomplete paradigm. The assumption is that a clinician would do nothing for 8 weeks before making adjustments in the management. However, if goals have not been achieved within a timely fashion, say within 2-6 weeks and depending upon the clinical urgency, the clinician is able to make adjustments, either by increase of the dose of monotherapy or by adding a second agent. The choice of which particular path will depend upon the particular clinical scenario. If one's first line response is to initiate combination therapy, one will never know whether the BP objectives for the particular patient would have been met with a monotherapy for instance. There has been simply no fair comparison of the proposed first line, fixed dose combination strategy and the strategy of careful dose and/or agent adjustment.

Thus the sponsor's claim to first-line treatment is totally reliant upon a short term, factorial study, 1235.1, in which study there was an inherent risk of being exposed to an unnecessarily high dose. The other two studies, 1235.5 and 1235.6, do nothing to support the claim to first line treatment as both studies were add-on studies, that is, studies conducted according to what has been long recognised as best clinical practice, that is careful dose titration to the desired effect. Both these studies were done in amlodipine non-responders. There was no add-on study in telmisartan non-responders.

The Delegate also had great concerns over the target group for initial or first line therapy, namely "*patients likely to need multiple antihypertensive agents to achieve their target BP goal*". How is a clinician expected to make a judgement of who is likely to need multiple antihypertensive agents? Certainly there is no advice in the proposed PI on this matter. However, as pointed out above, there is crucially no guard against the possibility of treatment with unnecessarily high doses of the combination or even unnecessary treatment with the combination as opposed to a monotherapy.

In summary, the submission supports a second line indication. However, there is no justification for first line treatment in a nebulously defined patient group, that is, those likely to need multiple antihypertensive agents to achieve their target BP goal and where there has been no fair comparison of that first line proposal against the strategy which it is meant to replace, that is careful dose and/or agent adjustment.

The Delegate proposed to approve the submission as replacement therapy or as add-on therapy in patients with hypertension, based on the quality, safety and efficacy of the product having been satisfactorily established for the indication below:

Treatment of hypertension

Treatment should not be initiated with this fixed-dose combination

The Delegate proposed to reject the submission as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals, based on the safety and efficacy of the product not having been satisfactorily established for the reasons stated above.

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

- The sponsor is requested to give a detailed commentary on the analyses which resulted in the estimates of the likelihood of achieving systolic and diastolic BP goals with the fixed-dose combination tablets. These appear to have been the basis for the inclusion in the US PI of the graphs in Figure 6 and would also appear to be the basis of the US approval of the FDC for initial treatment. Please comment on the latter also.
- The sponsor was requested to comment on a number of points concerning the graphical figures which show the estimates of likelihood in relation to baseline measurements of BP.
- Given that co-administration of an ARB is postulated to mitigate the occurrence of oedema caused by a CCB, it is surprising to note the rates of oedema in the FDC groups in trial 1235.5 were 6.2% in T40/A10 and 8.4% in T80/A10. One would have expected these results to have been reversed. The sponsor was requested to comment on this finding.
- The sponsor was asked to comment on the fact that there appears to be no notable difference in the predicted mean change from baseline between the three fixed-dose combinations involving the highest dose of amlodipine, that is, for the combinations telmisartan 20 mg/amlodipine 10 mg, telmisartan 40 mg/amlodipine 10 mg and telmisartan 80 mg/amlodipine 10 mg.
- In the open-label extension trial 1235.8, the proportion of patients with oedema increased from 10.3% (45/436) at the interim endpoint of trial 1235.6 to 15.4% (67/434). This was despite an up-titration in the dose of telmisartan and amlodipine fixed at its maximum dose, 10 mg. The sponsor was requested to comment.
- The sponsor was also requested to provide the most up-to-date analysis of the results of the ongoing open-label study, 1235.8.

The Delegate also directed the following questions to the ACPM.

- There is clear evidence that taking the fixed dose combination with food reduces the bioavailability of the telmisartan component in comparison with taking it in the fasting state. The bioavailability of the amlodipine component is not significantly affected. The sponsor has been asked to comment on this issue. The ACPM was also asked to express its opinion on the matter. For example, can this problem be resolved by appropriate advice in the PI?
- The ACPM was asked for its opinion on the absence of any add-on study in telmisartan non-responders. Does this represent a serious deficiency in the submission?
- Does the ACPM agree that there has been no fair comparison of the use of the fixed-dose combination as first-line therapy with the standard clinical approach of careful dose and/or agent adjustment? Does the ACPM agree with the Delegate that there has been insufficient evidence adduced to support the use of the fixed-dose combination as first-line therapy?

- Does the ACPM have any concerns over the tradename Twynsta with its similarity in sound to "Twinstar", the latter term implying excellence of some sort?

Response from Sponsor

Initial therapy. Delegate's proposed rejection on the basis of no fair comparison of the use of the FDC as first line therapy with standard approach of careful dose and/or agent adjustment:

The factorial design study (1235.1) was considered adequate to study the combination in a first-line setting. This study was considered pivotal by the FDA for approval of the first-line indication in the US. It was acknowledged that the Delegate's requested study directly comparing a first-line setting with an add-on approach has not been conducted. An indirect comparison of the factorial design study with the amlodipine non-responder studies could be done, however with the limitation of indirect comparisons.

According to current international guidelines, patients with a blood pressure (BP) 20/10 mmHg above their treatment target and/or patients with high cardiovascular (CV) risk are most likely in need of combination therapy to achieve their target and should be initiated with combination therapy.[12,13]

[12] Mancia et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC).Eur Heart J. 2007; 28:1462-1536.

[13] Chobanian et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289: 2560-2572.

Furthermore, it is widely accepted that low dose combination therapy is more effective than high dose monotherapy due to the synergistic and complementary mode of action.[14] In addition, not only reaching the BP target but also time to reach the target is considered relevant in terms of CV outcome. This has been shown in large cardiovascular outcome studies such as the VALUE study where the CCB amlodipine was compared to the ARB valsartan. Patients in the amlodipine arm reach their BP target earlier which translated into a better CV outcome.[15]

Nevertheless, the sponsor agreed to remove the first-line claim and revise the proposed indication as proposed by the Delegate, to as follows:

Treatment of hypertension. Treatment should not be initiated with this fixed-dose combination.

Add-on therapy. Delegate's comment on the absence of any add-on study in telmisartan non-responders:

It is acknowledged by the Delegate that the quality, safety and efficacy of Twynsta have been satisfactorily established as add-on therapy in patients with hypertension, and that the Delegate has no objections to a recommendation for use of Twynsta as second-line therapy (taking into account the evidence from the 3 pivotal studies 1235.1, 1235.5 and 1235.6).

In the factorial design study (1235.1), the BP efficacy of the key combinations telmisartan 40-80 mg plus amlodipine 5-10 mg (T40-80/A5-10) was superior to the respective monotherapy. This was also confirmed in the ABPM substudy.

From the results of 1235.1, the BP lowering efficacy of the respective monotherapy of A5-10 appears to be numerically better than T40-80. This is in line with other CCB plus ARB combinations as per the results reported in the Exforge (valsartan/amlodipine) PI and the Sevikar (olmesartan/amlodipine) PI.

Therefore, it is considered a reasonable approach to study the more effective component amlodipine in a non-responder setting and if the combination succeeds by adding the somewhat weaker component telmisartan, it can be assumed that this will also be the case by adding amlodipine to telmisartan non-responders. In addition, this approach reduces the number of patients being exposed to potentially insufficient treatment (that is, control arm with telmisartan monotherapy in patients that are not controlled on telmisartan).

Food effect on the bioavailability of the telmisartan component in the FDC:

The bioavailability study (1235.12) conducted with the FDC showed that administration of a high-fat meal with the T80/A10 decreased $AUC_{0-\infty}$ and C_{max} of telmisartan by 24.3% and 60.1%, respectively. A previous study that supported the registration of telmisartan monotherapy without any food intake restriction showed that a high-fat meal decreased $AUC_{0-\infty}$ and C_{max} of telmisartan taken alone at a dose of 160 mg (2 x 80 mg) by very similar values of 19% and 56%, respectively. The 80 mg dose was not included in that study but the 40 mg dose was, and it exhibited bioequivalence with respect to $AUC_{0-\infty}$ and a smaller reduction of C_{max} (25.6%) with food compared to that observed with the 80 mg dose in study 1235.12.

[14] Sica et al. Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats. Drugs 2002; 62: 443-462.

[15] Julius et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004; 363: 2022-2031.

In addition, a 4-week double blind, placebo-controlled, parallel-group study (502.235) was previously conducted to assess the magnitude and duration of the antihypertensive effect of telmisartan 40 mg or 80 mg administered once daily either with high fat food or fasted. This study showed that both doses of telmisartan given with food significantly reduced supine diastolic blood pressure in comparison to placebo.

Plasma concentration/effect analyses for telmisartan indicate that antihypertensive effects of telmisartan 40 mg, 80 mg and 120 mg are at the plateau region of the concentration-response curve. Based on results described above, telmisartan is approved in Australia and other countries worldwide for administration with and without food and without requiring a routine pattern for food intake.

This is in line with other approved drugs which show even lower bioavailability in the presence of food. Considering the flat dose response curve and the wide therapeutic range of telmisartan, the food effect on telmisartan pharmacokinetics observed in the study 1235.12 would translate into only minor differences with regard to the blood pressure lowering effect, which are not considered to be clinically relevant, neither for efficacy, nor for safety.

This is further supported by efficacy and safety results observed in the Phase III program of the telmisartan/amlodipine FDC (including the pivotal studies 1235.1, 1235.5 and 1235.6 and the supportive open-label follow-up trials 1235.7 and 1235.8), which permitted patients to take study medication with and without food and without a routine pattern. Nevertheless, a clinically meaningful and statistically significant blood pressure lowering effect was demonstrated in all studies for both females and males.

In summary, the observed effect of food on the bioavailability of telmisartan is not considered to be clinically relevant. Thus, the telmisartan/amlodipine FDC can be taken with and without food in accordance with the approved labelling for telmisartan taken as monotherapy. This fact has been accepted by the regulatory authorities in the US and EU, and Twynsta has been approved without any restriction with regards to food intake (Twynsta may be taken with or without food) in these respective countries.

Tradename. Delegate's comment on its similarity in sound to "Twinstar" (implying excellence)

The sponsor indicated it had not intended to imply excellence in the proposed tradename Twynsta. In its global name, safety research and marketing research conducted with healthcare professionals in key native English speaking countries, no connotation of any promotional messages were found in association with the proposed tradename.

Furthermore, the sponsor wished to highlight to the ACPM and the Delegate that the proposed tradename Twynsta has been accepted by major regulatory authorities worldwide including the US, EU, Canada and Switzerland. No issues were raised concerning an evocation of "sta" to impart an impression of "star" and of excellence or superiority. Given the worldwide regulatory acceptance of the tradename Twynsta, Boehringer Ingelheim strongly considered that the same tradename Twynsta should be accepted and approved for the telmisartan/amlodipine FDC in Australia.

Analyses and graphical figures for the estimates of the likelihood of achieving systolic and diastolic BP goals with the FDC tablets (in US PI) and basis of the US approval of the FDC for the initial treatment.

It is correct that the figures presenting the likelihood of achieving systolic and diastolic goals with the fixed dose combinations were generated from post-hoc analyses of trial 1235.1. These analyses were performed according to recommendations of the FDA which are

summarised in the guidance document "Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs". This guidance document has been established by the FDA for approval of first-line indication based on the graphs of the probability of achieving BP goals relative to baseline blood pressure.

As these recommendations only became available after the un-blinding of trial 1235.1, the analyses could not be included in the statistical analysis plan of the study. However, the robustness of the curves describing the likelihood of goal achievement depending on baseline blood pressure was extensively tested using non-parametric local regression, diagnostic tests and other descriptive measures like histograms.

On request of the FDA reviewers (clinicians and statisticians), a few patients with high blood pressure values in some of the treatment groups were removed from the calculations and graphical presentation.

The sponsor did not see any discrepancy between the graphical figures and the results displayed in the tables of the clinical evaluation report. For all criteria, the percentage of patients with goal achievement is higher for the combination treatment compared to the mono treatments, and in most of the cases, the advantage was even statistically significant, although the study was not powered to demonstrate an advantage of each combination over its components for these specific endpoints.

It was acknowledged that the estimates towards the right tail of each curve have wider confidence intervals and are less precise. Nevertheless, the graphical figures give a clear indication to the practitioner that the likelihood of success is not only depending on the treatment, but also on the baseline blood pressure of the patient, and that the combination of telmisartan and amlodipine especially offers an advantage over therapy with the mono-components.

The FDA statistical review evaluated the consistency of the analyses with the guidance document "Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs" and judged that the study support the combination therapy for use as an initial therapy indication in patients with higher blood pressure baselines who are likely to need multiple drugs to achieve their BP goals.

Occurrence of oedema in the FDC groups in trial 1235.6, 6.2% in T40/A10 and 8.4% in T80/A10 despite the postulation that co-administration of an ARB mitigates the occurrence of oedema caused by a CCB:

It was acknowledged by the Delegate that due to the design of the study, a substantial number of patients who did not tolerate amlodipine monotherapy discontinued during the run in phase (16.6% of patients experienced peripheral oedema of which about 1/3 discontinued during the run-in phase). Thus, patients with intolerance to amlodipine 10 mg (A10) were excluded from randomisation to either of the 3 treatment arms. The overall incidence of peripheral oedema with the combination of telmisartan 40-80 mg (T40-80) plus A10 was numerically lower to what has been observed in other studies most likely due to the fact that the study design selected patients who tolerated A10. Although one would expect that patients receiving the T80/A10 combination have a lower number of peripheral oedema compared to T40/A10, it was acknowledged that the study was not adequately designed and powered to show a difference between the two treatment regimens. Thus, the finding is considered a chance finding due to the rather low overall incidence of peripheral oedema in the randomised part of this study.

There appears to be no notable difference in the predicted mean change from baseline between the three FDCs involving the highest dose of amlodipine, that is, for the combinations T20/A10, T40/A10 and T80/A10:

Amlodipine 10 mg is a very effective blood pressure lowering dose and telmisartan has a shallow dose response relationship regarding its blood pressure lowering efficacy.

However, it should be considered that the studies in this application were not designed to demonstrate differences between T40/A10 and T80/A10. According to the EMA Scientific Advice given to the sponsor on 26 January 2006, the two filter design studies, 1235.5 and 1235.6, would be sufficient to register the proposed FDC products. There was no requirement for a direct comparison between T40/A10 and T80/A10. Furthermore, Boehringer Ingelheim was also of the opinion that the T80/A10 strength can be used for replacement therapy (that is, to switch patients receiving telmisartan 80 mg and amlodipine 10 mg from separate tablets to this FDC), in addition to use for up-titration to attain additional blood pressure lowering. Data to support the additional blood pressure lowering beyond that achieved with T40/A10 was also provided.

1. Additional BP reductions and BP control in patients not controlled on T40/A10 in the 1235.6 follow-up study (1235.8):

In the completed 1235.8 study (follow-up of 1235.6), 91 patients receiving T40/A10 were up-titrated to T80/A10 at week 8 due to inadequate BP control and did not receive any further antihypertensive add-on medication by the end of the trial. At the end of the study (34 weeks), 72 (79.1%) of these patients achieved diastolic BP (DBP) control (<90 mmHg). The patients who were up-titrated to T80/A10 achieved an additional mean BP reduction, from the end of study 1235.6 measures, of -6.6/-5.5 mmHg (SBP/DBP), whereas patients who stayed on T40/A10 achieved mean BP reductions of -4.7/-4.4 mmHg (SBP/DBP).

With regard to the effect of up-titration from T40/A10 to T80/A10 at the 8 week visit, the additional blood pressure reduction achieved on T80/A10 by the next visit (6 weeks following up-titration) was -6.1/-4.8 mmHg SBP/DBP. This effect was maintained with comparable magnitude up to the last visit on T80/A10 without other antihypertensive add-on medication.

2. 24-hour ABPM reductions and control rates in patients receiving T40/A10 or T80/A10 in the factorial design study (1235.1):

The most accurate and reproducible means of detecting blood pressure treatment differences can be demonstrated with ABPM. In the ABPM substudy of 1235.1, 57 patients received T40/A10 and 52 patients received T80/A10. At study end (8 weeks), the placebo corrected 24-hour mean changes from baseline was -19.1/-12.9 mmHg (SBP/DBP) and -21.0/-14.3 mmHg (SBP/DBP) for T40/A10 and T80/A10, respectively, in the overall population; and -17.8/-12.3 mmHg and -19.7/-14.0 mmHg for T40/A10 and T80/A10, respectively, in patients with at least moderate hypertension (DBP $\geq$100 mmHg).

The placebo corrected mean reduction of the last 6 hours of the 24-hour interval for the overall population was -19.8/-12.1 mmHg and -23.7/-15.9 for T40/A10 and T80/A10, respectively. Furthermore, the 24-hour ABPM control rates (defined as a target of <130/80 mmHg for normal 24-hour mean ABPM as per A.H.A. recommendation were, for SBP, 68.4% and 82.7% and for DBP, 80.7% and 92.3%, for T40/A10 and T80/A10, respectively.[16]

[16] Pickering TG et al., Recommendations for Blood Pressure Measurement in Humans and Experimental Animals. Circulation 2005; 111: 697-716.

The differences between the two dose strengths of telmisartan 40 and 80 mg plus amlodipine are considered clinically relevant, if one takes into account the findings of the large hypertension treatment meta-analysis which showed that even a 2 mmHg lower SBP would lead to a 10% lower stroke mortality and a 7% lower mortality from ischemic disease over 10 years.

Occurrence of oedema in open-label extension trial 1235.8 . The proportion of patients with oedema increased from 10.3% (45/436) at the interim endpoint of trial 1235.6 to 15.4% (67/434) despite an up-titration in the dose of telmisartan and amlodipine fixed at its maximum dose, 10 mg.

According to the final study results of the completed open-label extension trial 1235.8, 10.1% (84/835) of patients who had entered the follow-up trial 1235.8 already had experienced oedema in the preceding trial 1235.6. Until the end of trial 1235.8, 15.2% (126/828) of all patients had oedema. Note that the time of exposure was different in trials 1235.6 and 1235.8. The total exposure in trial 1235.6 was 148.3 patient-years. During the conduct of the follow-up trial 1235.8 with a total exposure of 542.7 patient-years, only 42 additional patients with oedema were counted. Thus, taking into account the length of the trials, 56.6 patients with oedema per 100 patient-years were observed during trial 1235.6, whereas only 7.7 patients with oedema per 100 patient-years were observed during trial 1235.8.

For the most frequent type of oedema (peripheral oedema), the number of patients affected in trial 1235.8 (broken down to treatment doses) were: T40/A10: 18 patients (2.1%), 8.9 patients per 100 patient-years; T80/A10: 27 patients (4.4%), 8.0 patients per 100 patient-years. Note that some patients had oedema on different treatments; hence the sum over treatments is greater than the total of all patients with oedema.

Most of these cases were considered drug-related: T40/A10: 16 patients (1.9%), 7.9 patients per 100 patient-years; T80/A10: 24 patients (3.9%), 7.1 patients per 100 patient-years. In the preceding trial 1235.6, the respective numbers for peripheral oedema were: A10: 22 patients (7.0%); T40/A10: 21 patients (6.7%); T80/A10: 27 patients (8.5%) of which 6.3%, 5.4 and 6.9% were considered drug related and 1.9, 1.0 and 0.6% of patients discontinued treatment due to peripheral oedema, respectively.

In summary, the incidence of peripheral oedema was lower in the follow-up trial 1235.8 compared to the preceding trial 1235.6. This may be due to adaptation to treatment over time or the switch from A10 monotherapy (in trial 1235.6) to a combination with telmisartan (in trial 1235.8). When adjusted for exposure the incidence of peripheral oedema was numerically lower with T80/A10 vs. T40/A10 in trial 1235.8 (i.e. 8.0 vs. 8.9 patients per 100 patient-years, respectively).

Most up-to-date analysis of the results of the ongoing open-label study, 1235.8.

A brief summary of the main efficacy and safety (oedema) results of the completed open-label trial 1235.8 were presented in the responses above. The synopsis of the final clinical trial report was also provided.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended approval for the indication:

Treatment of hypertension.

Treatment should not be initiated with this fixed-dose combination.

It was noted by ACPM that the sponsor had withdrawn their original request for initial therapy of hypertension.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Twynsta tablets containing telmisartan / amlodipine (as besylate) 40/5 mg, 40/10 mg, 80/5 mg and 80/10 mg for the indication:

Treatment of hypertension. Treatment should not be initiated with this fixed-dose combination. (See Dosage and Administration)

Attachment 1. Product Information

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

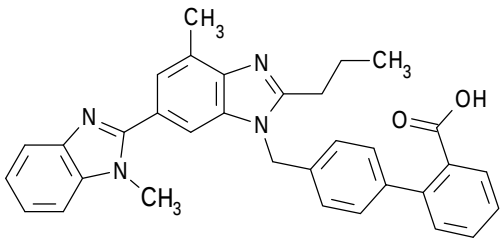
TWYNSTA®

(Telmisartan/Amlodipine)

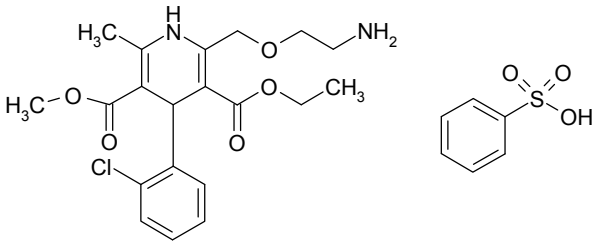
NAME OF THE MEDICINE

TWYNSTA contains the active ingredients telmisartan and amlodipine (as the besylate salt).

Structural formula:



Telmisartan



and enantiomer

Amlodipine (as the besylate salt)

Chemical name:

4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)-methyl]-[1,1'-biphenyl]-2-carboxylic acid

Molecular formula: $C_{33}H_{30}N_4O_2$

CAS number: 144701-48-4

Molecular weight: 514.6

Chemical name:

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

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

CAS number: 111470-99-6

Molecular weight: 567.1

DESCRIPTION

Telmisartan is an off-white to yellowish crystalline powder. It is practically insoluble in water, very slightly soluble in ethanol, slightly soluble in methanol and soluble in a mixture of chloroform and methanol (1:1).

Amlodipine besylate is a white or almost white powder that is slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and slightly soluble in 2-propanol.

TWYNSTA is available in four tablet strengths for oral administration, containing 40 mg or 80 mg telmisartan and 5 mg or 10 mg amlodipine (as the besylate salt), in the following combinations:

- TWYNSTA 40/5 mg containing telmisartan 40 mg/amlodipine 5 mg
- TWYNSTA 40/10 mg containing telmisartan 40 mg/amlodipine 10 mg
- TWYNSTA 80/5 mg containing telmisartan 80 mg/amlodipine 5 mg
- TWYNSTA 80/10 mg containing telmisartan 80 mg/amlodipine 10 mg

Excipients: Each TWYNSTA tablet also contains sodium hydroxide, povidone, meglumine, sorbitol, magnesium stearate, cellulose – microcrystalline, starch – pregelatinised maize, starch – maize, silica – colloidal anhydrous and Pigment Blend PB-57699 as colouring agent.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: angiotensin II antagonists, plain (telmisartan) combinations with dihydropyridine derivatives (amlodipine).

Mechanism of action

TWYNSTA combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine.

The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

TWYNSTA once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Telmisartan

Telmisartan is an orally effective and specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor and does not reveal relevant affinity for other receptors nor does it inhibit human plasma renin or block ion channels. The clinically relevant effect of AT_1 receptor blockade is to lower blood pressure by inhibition of angiotensin II mediated vasoconstriction leading to reduction of systemic vascular resistance. During administration with telmisartan, removal of angiotensin II negative feedback on renin secretion results in increased plasma renin activity, which in turn leads to increases in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppressed aldosterone levels indicate effective angiotensin II receptor blockade. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse effects or cause oedema.

In humans, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked increase in blood pressure. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

After administration of the first dose of telmisartan, onset of antihypertensive activity occurs gradually within 3 hours. The maximal reduction in blood pressure is generally attained 4-8 weeks after the start of treatment and is sustained during the long-term therapy.

The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. With ambulatory blood pressure monitoring and conventional blood pressure measurements, the 24 hour trough to peak ratio was consistently above 80% for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) after doses of 40 mg and 80 mg of telmisartan in placebo controlled clinical studies.

In patients with hypertension, telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The antihypertensive efficacy of telmisartan is independent of gender or age, and is comparable to that of agents representative of other classes of antihypertensive drugs (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, ramipril, hydrochlorothiazide, lisinopril and valsartan).

Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

Telmisartan treatment has been shown in clinical trials to be associated with statistically significant reductions in Left Ventricular Mass and Left Ventricular Mass Index in patients with hypertension and Left Ventricular Hypertrophy.

The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

Prevention of cardiovascular morbidity and mortality

ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, transient ischaemic attack, peripheral vascular disease, or diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which represents a broad cross-section of patients at high risk of cardiovascular events.

The co-primary objectives of the ONTARGET trial were to determine if (a) the combination of telmisartan 80 mg and ramipril 10 mg is superior to ramipril 10 mg alone and if (b) telmisartan 80 mg is not inferior to ramipril 10 mg alone in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure. Hypothesis tests were performed using hazard ratios and time-to-event analyses (Kaplan-Meier).

The principal patient exclusion criteria included: symptomatic heart failure or other specific cardiac diseases, syncopal episodes of unknown aetiology or planned cardiac surgery within 3 months of the start of study, uncontrolled hypertension or haemorrhagic stroke.

Patients were randomised to one of the three following treatment groups: telmisartan 80 mg (n=8542), ramipril 10 mg (n=8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n=8502), and followed for a mean observation time of 4.5 years. The population studied was 73% male, 74% Caucasian, 14% Asian and 43% were 65 years of age or older. Hypertension was present in nearly 83% of randomised patients: 69% of patients had a history of hypertension at randomisation and an additional 14% had actual blood pressure readings ≥ 140/90 mm Hg. At baseline, the total percentage of patients with a medical history of diabetes was 38% and an additional 3% presented with elevated fasting plasma glucose levels. Baseline therapy included acetylsalicylic acid (76%), statins (62%), beta-blockers (57%), calcium channel blockers (34%), nitrates (29%) and diuretics (28%).

Adherence to treatment was better for telmisartan than for ramipril or the combination of telmisartan and ramipril, although the study population had been pre-screened for tolerance to treatment with an ACE-inhibitor. During the study, significantly less telmisartan patients (22.0%) discontinued treatment, compared to ramipril patients (24.4%) and telmisartan/ramipril patients (25.3%). The analysis of adverse events leading to permanent treatment discontinuation and of serious adverse events showed that cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Comparison of telmisartan versus ramipril: The choice of the non-inferiority margin of 1.13 was solely based on the results of the HOPE (Heart Outcomes Prevention Evaluation) study. Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7%) and ramipril (16.5%) groups. In the intention-to-treat (ITT) analysis, the hazard ratio for telmisartan versus ramipril was 1.01 (97.5% CI 0.93-1.10, p(non-inferiority)=0.0019). The

non-inferiority result was confirmed in the per-protocol (PP) analysis, where the hazard ratio was 1.02 (97.5% CI 0.93-1.12, p (non-inferiority) =0.0078). Since the upper limit of the 97.5% CI was below the pre-defined non-inferiority margin of 1.13 and the p-value for non-inferiority was below 0.0125 in both the ITT and PP analyses, the trial succeeded in demonstrating the non-inferiority of telmisartan versus ramipril in the prevention of the composite primary endpoint. The non-inferiority conclusion was found to persist following corrections for differences in systolic blood pressure at baseline and over time. There was no difference in the primary endpoint in subgroups based on age, gender, race, baseline concomitant therapies or underlying diseases.

Telmisartan was also found to be similarly effective to ramipril in several pre-specified secondary endpoints, including a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, the primary endpoint in the reference study HOPE, which had investigated the effect of ramipril versus placebo. The ITT hazard ratio of telmisartan versus ramipril for this endpoint in ONTARGET was 0.99 (97.5% CI 0.90-1.08, p(non-inferiority)=0.0004), and confirmed by the PP hazard ratio of 1.00 (97.5% CI 0.91-1.11, p(non-inferiority)=0.0041.

Comparison of telmisartan plus ramipril combination versus ramipril monotherapy alone: Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone, thus superiority of the combination could not be demonstrated. . The incidence of the primary endpoint was 16.3% in the telmisartan plus ramipril combination group, compared to the telmisartan (16.7%) and ramipril (16.5%) groups. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination group. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx 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, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

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.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with heart failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Pharmacokinetics

Pharmacokinetics of the Fixed Dose Combination:

The rate and extent of absorption of TWYNSTA are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

The bioavailability study (1235.12) conducted with the fixed dose combination showed that administration of a high-fat meal with the TWYNSTA 80/10 mg tablet decreased the total area under the plasma concentration-time curve (AUC) and Cmax for telmisartan by about 24% and 60%, respectively. For amlodipine, AUC and Cmax were not altered (see DOSAGE AND ADMINISTRATION). However, considering the flat dose response curve and the wide therapeutic range of telmisartan, the food effect on telmisartan pharmacokinetics observed in the study 1235.12 would translate into only minor differences with regard to the blood pressure lowering effect, which are not considered to be clinically relevant, neither for efficacy, nor for safety.Pharmacokinetics of the single components:

Absorption

Telmisartan: Following oral administration of telmisartan, absorption is rapid (t_{max} ranges from 0.5 to 2 hours) although the amount absorbed varies. Absolute bioavailability of telmisartan was shown to be dose dependent. The mean absolute bioavailability of 40 mg telmisartan was 40%, whereas the mean absolute bioavailability of the 160 mg dose amounted to about 60%.

When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC0-∞) of telmisartan varies from approximately 6% (40 mg dose) to approximately 19% (160 mg dose). The small reduction in AUC should not cause a reduction in the therapeutic efficacy. Therefore, telmisartan may be taken with or without food.

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.

Distribution

Telmisartan: Telmisartan is highly bound to plasma protein (>99.5%), mainly albumin and alpha-1-acid glycoprotein. The mean steady state apparent volume of distribution (Vdss) is approximately 6.6 L/kg.

Amlodipine: The volume of distribution of amlodipine is approximately 21 L/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drugs is bound to plasma proteins in hypertensive patients.

Metabolism

Telmisartan: Telmisartan undergoes substantial first-pass metabolism by conjugation to the acylglucuronide. No pharmacological activity has been shown for the conjugate. Telmisartan is not metabolised by the cytochrome P450 system.

Amlodipine: Amlodipine is extensive (approximately 90%) metabolised by the liver to inactive metabolites.

Elimination

Telmisartan: Telmisartan is characterised by bi-exponential decay pharmacokinetics with a terminal elimination half-life of 18.3-23.0 hours.

The maximum plasma concentration (C_{max}) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose interval.

After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1% of dose.

Amlodipine: Amlodipine elimination from the plasma is biphasic, with a termination elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7-8 days. 10% of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Pharmacokinetics in special patient groups:

Children (age below 18 years)

No pharmacokinetic data are available in the paediatric population.

Elderly

Telmisartan: The pharmacokinetics of telmisartan do not differ between younger and elderly patients (i.e. patients older than 65 years of age).

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

Gender

Telmisartan: Plasma concentrations are generally 2-3 times higher in females than in males. In clinical trials, however, no clinically significant increases in blood pressure response or incidences of orthostatic hypotension were found in females. No dosage adjustment is necessary.

Patients with renal impairment

Telmisartan: Lower plasma concentrations were observed in patients with renal insufficiency (creatinine clearance 30-80 mL/min) undergoing dialysis, however, this has proved not to be of clinical significance. Telmisartan is highly bound to plasma proteins in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Amlodipine: The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Patients with hepatic impairment

Telmisartan: Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100%. The elimination half-life is not changed in patients with hepatic impairment.

Amlodipine: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC.

CLINICAL TRIALS

TWYNSTA

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

The efficacy of TWYNSTA for treatment of hypertension was studied in over 3400 patients in three pivotal randomised double-blind studies (one placebo-controlled and two active-controlled trials) and over 1400 patients in two supportive open-label follow-up trials. Adults with mild to severe uncomplicated essential hypertension (mean seated diastolic blood pressure ≥95 mmHg and <119 mmHg) were enrolled in the placebo-controlled trial. In the two active-controlled trials, adult patients with mean seated diastolic blood pressure ≥95 mmHg (if on antihypertensive treatment) or ≥100 mmHg (if not treated with an antihypertensive) and also did not respond adequately (mean seated diastolic blood pressure ≥90 mmHg) after 6 weeks of open-label amlodipine monotherapy were enrolled. Exclusion criteria for the trials were consistent with the contraindications in the Product Information, and the conditions listed in the precautions. Patients with secondary hypertension, uncontrolled hypertension, symptomatic congestive heart failure were excluded. No study was conducted specifically in telmisartan non-responders. The efficacy and safety of TWYNSTA compared to telmisartan monotherapy was demonstrated in the pivotal placebo-controlled, parallel group factorial study.

In the 8-week multicenter, randomised, double-blind, placebo-controlled, parallel group factorial study, 1461 patients with mild to severe hypertension (mean baseline seated systolic/diastolic diastolic blood pressure 153.2/101.8 mmHg) underwent a 3-4 week placebo run-in period in order to wash out all antihypertensive medications before they were randomised to a double-blind active treatment. Treatment with each combination dose of TWYNSTA resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

The telmisartan/amlodipine combinations showed dose-related reductions in systolic/diastolic blood pressure across the therapeutic dose range: -21.8/-16.5 mmHg with 40/5 mg; -22.1/-18.2 mmHg with 80/5 mg; -24.7/-20.2 mmHg with 40/10 mg; -26.4/-20.1 mmHg with 80/10 mg.

The proportions of patients reaching a diastolic blood pressure <90 mmHg with a telmisartan/amlodipine combination were: 71.6% with 40/5 mg; 74.8% with 80/5 mg; 82.1% with 40/10 mg; 85.3% with 80/10 mg.

A subset of 1050 patients in the study had moderate to severe hypertension (DBP ≥100 mmHg). In these patients who are likely to need more than one antihypertensive agent to achieve blood pressure goal, the mean changes in systolic/diastolic blood pressure with a combination therapy containing amlodipine 5 mg (-22.2/-17.2 mmHg with 40/5 mg; -22.5/-19.1 mmHg with 80/5 mg) were comparable to or greater than those seen with amlodipine 10 mg (-21.0/-17.6 mmHg).

The majority of the antihypertensive effect was attained within 2 weeks after initiation of therapy.

Automated ambulatory blood pressure monitoring (ABPM) performed in a subset of 562 patients confirmed the results seen with in-clinic systolic and diastolic blood pressure reductions consistently over the entire 24-hours dosing period.

In a further multicentre, double-blind, active-controlled study, a total of 1097 patients with mild to severe hypertension (mean seated baseline systolic/diastolic blood pressure 149.5/96.6 mmHg) who were not adequately controlled on amlodipine 5 mg received TWYNSTA (40/5 mg or 80/5 mg) or amlodipine alone (5 mg or 10 mg). After 8 weeks of treatment, each of the combination was statistically significantly superior to both amlodipine monotherapy doses in reducing systolic and diastolic blood pressures: -13.6/-9.4 mmHg with TWYNSTA 40/5 mg; -15.0/-10.6 mmHg with TWYNSTA 80/5 mg; -6.2/-5.7 mmHg with amlodipine 5 mg; -11.1/-8.0 mmHg with amlodipine 10 mg.

The proportions of patients with normalisation of blood pressure (trough seated diastolic blood pressure <90 mmHg at the end of the trial) were: 56.7% with TWYNSTA 40/5 mg and 63.8% with TWYNSTA 80/5 mg compared to 42.0% with amlodipine 5 mg and 56.7% with amlodipine 10 mg.

Oedema related events (peripheral oedema, generalised oedema, and oedema) were significantly lower in patients who received TWYNSTA (40/5 mg or 80/5 mg) as compared to patients who received amlodipine 10 mg (4.4% vs. 24.9%, respectively).

In another multicentre, double-blind, active-controlled study, a total of 947 patients with mild to severe hypertension (mean seated baseline systolic/diastolic blood pressure 147.5/95.6 mmHg) who were not adequately controlled on amlodipine 10 mg received TWYNSTA (40/10 mg or 80/10 mg) or amlodipine alone (10 mg). After 8 weeks, each of the combination treatments was statistically significantly superior to amlodipine monotherapy in reducing diastolic and systolic blood pressures: -11.1/-9.2 mmHg with TWYNSTA 40/10 mg, -11.3/-9.3 mmHg with TWYNSTA 80/10 mg; -7.4/-6.5 mmHg with amlodipine 10 mg.

The proportions of patients with normalisation of blood pressure (trough seated diastolic blood pressure <90 mmHg at the end of the trial) were 63.7% with TWYNSTA 40/10 mg and 66.5% with TWYNSTA 80/10 mg compared to 51.1% with amlodipine 10 mg.

In two corresponding open-label long-term follow up studies performed over a further 6 months the effect of TWYNSTA was maintained over the trial period.

In patients not adequately controlled on amlodipine 5 mg, TWYNSTA achieved similar (40/5 mg) or better (80/5mg) blood pressure control compared to amlodipine 10 mg with significantly less oedema.

In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, TWYNSTA 40/5 mg or 80/5 mg may achieve similar blood pressure control with less oedema.

The antihypertensive effect of TWYNSTA was similar irrespective of age and gender, and was similar in patients with and without diabetes.

TWYNSTA has not been studied in any patient population other than hypertension. Telmisartan has been studied in a large outcome study in 25620 patients with high cardiovascular risk (ONTARGET). Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease. (see also PHARMACOLOGY)

INDICATIONS

Treatment of hypertension. Treatment should not be initiated with this fixed-dose combination. (see DOSAGE AND ADMINISTRATION)

CONTRAINDICATIONS

- Hypersensitivity to the active ingredients or to any of the excipients
- Hypersensitivity to dihydropyridine derivatives
- Pregnancy
- Lactation
- Biliary obstructive disorders
- Severe hepatic impairment
- Cardiogenic shock

In case of rare hereditary conditions that may be incompatible with an excipient of the product, the use of the product is contraindicated (see PRECAUTIONS).

PRECAUTIONS

Hepatic impairment

Telmisartan: Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or severe hepatic insufficiency can be expected to have reduced clearance. TWYNSTA is therefore, contraindicated for use in these patients.

TWYNSTA should only be used with caution in patients with mild to moderate hepatic impairment (see DOSAGE AND ADMINISTRATION).

Amlodipine: As with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. Worsening of liver function test values may occur. Amlodipine should therefore be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see DOSAGE AND ADMINISTRATION).

TWYNSTA should therefore be used with caution in these patients.

Renovascular hypertension

Telmisartan: There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Increases in serum creatinine have been observed in studies with ACE-inhibitors in patients with single or bilateral renal artery stenosis. An effect similar to that observed with ACE inhibitors should be anticipated with TWYNSTA.

Renal impairment and kidney transplantation

When TWYNSTA is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended.

There is no experience regarding the administration of TWYNSTA in patients with a recent kidney transplant.

Telmisartan: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. Telmisartan is not dialysable.

Amlodipine: Amlodipine is extensively metabolised to inactive metabolites with 10% excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine may be used in such patients at normal doses. Amlodipine is not dialysable.

Intravascular hypovolaemia

Telmisartan: Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by e.g. vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of TWYNSTA.

Dual blockade of the renin-angiotensin-aldosterone system

Telmisartan: As a consequence of inhibiting the renin-angiotensin-aldosterone system changes in renal function (including acute renal failure) have been reported in susceptible individuals,

especially if combining medicinal products that affect this system. TWYNSTA can be administered with other antihypertensive drugs, however dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to an angiotensin II receptor antagonist) is not recommended and should therefore be limited to individually defined cases with close monitoring of renal function.

In the ONTARGET trial, patients receiving the combination of telmisartan and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of hyperkalaemia, renal failure, hypotension and syncope compared with groups receiving telmisartan alone or ramipril alone (see Interactions with other medicines). Concomitant use of TWYNSTA and ramipril is therefore not recommended in patients with already controlled blood pressure.

Other conditions with stimulation of the renin-angiotensin-aldosterone system

Telmisartan: In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products (e.g. angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure and/or death.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE-inhibitor or angiotensin receptor antagonist, an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.Primary aldosteronism

Telmisartan: Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

Both telmisartan and amlodipine: As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Unstable angina pectoris, acute myocardial infarction

There are no data to support the use of TWYNSTA in unstable angina pectoris and during or within one month of a myocardial infarction.

Amlodipine: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Beta-blocker withdrawal

Amlodipine: Amlodipine is not a beta-blocker and therefore provides no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Heart failure

Amlodipine: In general, calcium channel blockers should be used with caution in patients with heart failure. 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.

Hyperkalaemia

Telmisartan: During treatment with medicinal products that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended.

Based on experience with the use of medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (e.g. heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with telmisartan.

Sorbitol

TWYNSTA tablets contain 337.28 mg of sorbitol per maximum recommended daily dose. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

Ethnical differences

TWYNSTA was effective when treating black patients (usually a low-renin population). The magnitude of blood pressure lowering in black patients approached that observed in non-black patients

Other

Telmisartan: As observed for angiotensin converting enzyme inhibitors, angiotensin receptor antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Use in pregnancy (Category D)

The effects of TWYNSTA during pregnancy are not known. Nonclinical studies investigating the reproductive toxicity of TWYNSTA have not been conducted. Effects related to the individual components are described below.

Telmisartan: Angiotensin II receptor antagonists should not be initiated during pregnancy. The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimester of pregnancy.

Although there is no clinical experience with telmisartan in pregnant women, *in utero* exposure to drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and even death. Several dozen cases have been reported in the world literature in patients who

were taking angiotensin converting enzyme inhibitors. Therefore, when pregnancy is detected, telmisartan should be discontinued as soon as possible.

Angiotensin II receptor antagonists exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Oligohydramnios reported in this setting, presumably resulting from decreased fetal renal function, has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to occur when drug exposure has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Women of child-bearing age should be warned of the potential hazards to their fetus should they become pregnant.

Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension, oliguria and hyperkalaemia.

Preclinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity. Telmisartan has been shown to cross the placenta in rats. There were no teratogenic effects when telmisartan was administered orally to rats and rabbits during the period of organogenesis at doses up to 50 and 45 mg/kg/day, respectively. However, fetal resorptions were observed at the highest dose level in rabbits. Administration of 50 mg/kg/day telmisartan to rats during pregnancy and lactation caused a decrease in birth weight and suppression of postnatal growth and development of the offspring. The no-effect dose level in rabbits was 15 mg/kg/day, and corresponded to a plasma AUC value that was about 9 times higher than that anticipated in women at the highest recommended dose. Plasma drug levels were not measured at the high dose level in rats, but data from other studies suggest that they would have been similar to those in women at the maximum recommended dose.

Amlodipine: Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, these drugs carry the potential to produce fetal hypoxia associated with maternal hypotension, and there may be a risk of prolonged delivery.

In reproductive toxicity studies in rats, delayed parturition, difficult labour and impaired fetal and pup survival were seen after oral administration at 10 mg/kg amlodipine besylate.

Effects on fertility

Since the non-clinical toxicity profiles of telmisartan and amlodipine are not overlapping, no exacerbation of toxicity was expected for the combination.

Nonclinical studies investigating the reproductive toxicity of TWYNSTA have not been conducted. Nonclinical data available for the components of this fixed dose combination are reported below.

Telmisartan: Fertility of male and female rats was unaffected at oral telmisartan doses up to 100 mg/kg/day.

Amlodipine: There was no effect on the fertility of rats treated orally at doses of up to 18 mg/kg/day (about 16 times the MRHD of 10 mg/day on a mg/m^2 basis).

Use in lactation

TWYNSTA is contraindicated during lactation, since it is not known whether telmisartan and/or amlodipine are excreted in human milk. Nonclinical studies investigating the effects of TWYNSTA during lactation have not been conducted.

Animal studies have shown excretion of telmisartan in breast milk. When administered orally to lactating rats at 50 mg/kg/day, telmisartan suppressed postnatal growth and development of the offspring.

Lactating women should either not be prescribed TWYNSTA or should discontinue breastfeeding if TWYNSTA is administered.

Use in children

TWYNSTA is not recommended for us in patients aged below 18 years due to lack of data on safety and efficacy.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as syncope, somnolence, dizziness, or vertigo during treatment. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience these adverse experiences, they should avoid potentially hazardous tasks such as driving or operating machinery.

Carcinogenicity

No carcinogenicity studies have been conducted with the telmisartan/amlodipine combination. Nonclinical data available for the individual components are reported below.

Telmisartan: There was no evidence of carcinogenicity in rats and mice. Two-year studies in mice and rats did not show any increases in tumour incidences when telmisartan was administered in the diet at doses up to 1000 and 100 mg/kg/day, respectively. Plasma AUC values at the highest dose levels were approximately 60 and 15 times greater, respectively, than those anticipated in humans at the maximum recommended dose.

Amlodipine: Preclinical data reveal no special hazard for humans based on conventional studies of carcinogenic potential. Amlodipine did not induce tumours in rats at oral doses up to 2.5 mg/kg (plasma levels similar to those achieved clinically).

Genotoxicity

No genotoxicity studies have been conducted with the telmisartan/amlodipine combination. Nonclinical data available for the individual components are reported below.

Telmisartan: Telmisartan was not genotoxic in a battery of tests for gene mutations and clastogenicity.

Amlodipine: Amlodipine was not genotoxic in a battery of tests for gene mutations and clastogenicity.

Interactions with other medicines

No interactions between the two components of this fixed dose combinations have been observed in clinical studies.

Interactions common to the combination

No drug interaction studies have been conducted with TWYNSTA and other medicinal products.

Concomitant use to be taken into account

Other antihypertensive agents: The blood pressure lowering effect of TWYNSTA can be increased by concomitant use of other antihypertensive medicinal products and vice versa.

Agents with blood pressure lowering potential: Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including TWYNSTA, e.g. baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route): Reduction of the antihypertensive effect.

Interactions linked to telmisartan

Concomitant use to be taken into account

Other antihypertensive agents: Telmisartan may increase the hypotensive effect of other antihypertensive agents.

Others: Other interactions of clinical significance have not been identified. Co-administration of telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine. For digoxin a 20% increase in median plasma digoxin trough concentration has been observed (39% in a single case), monitoring of plasma digoxin levels should be considered particularly when initiating, adjusting or discontinuing concomitant TWYNSTA.

Concomitant use requiring caution

Non-steroidal anti-inflammatory drugs (NSAIDs): Treatment with NSAIDs (i.e. aspirin at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the renin-angiotensin-system like telmisartan may have synergistic effects. Patients receiving NSAIDs and telmisartan should be adequately hydrated and be monitored for renal function at the beginning of combined treatment. A reduced effect of antihypertensive drugs like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

Ramipril: In one study, the co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1 fold, respectively, and C_{max} and AUC of ramipril at 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16% respectively. The clinical relevance of this observation is not fully known. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamics effects of the combined drugs and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Combining telmisartan with ramipril in the ONTARGET trial resulted in a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope compared to telmisartan alone or ramipril alone (see PHARMACOLOGY, Pharmacodynamics, telmisartan). Concomitant use of telmisartan and ramipril is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Cases have also been reported with angiotensin II receptor antagonists including telmisartan. Therefore, serum lithium level monitoring is advisable during concomitant use.

Interactions linked to amlodipine

Concomitant use requiring caution

Grapefruit and grapefruit juice: Administration of TWYNSTA with grapefruit or grapefruit juice is not recommended since bioavailability may be increased in certain patients resulting in increased blood pressure lowering effects.

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. Amlodipine should be used with caution together with CYP3A4 inhibitors.

CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, phosphenytoin, 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. Amlodipine should be used with caution together with CYP3A4 inducers.

Concomitant use to be taken into account

Others: In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, aluminium/magnesium antacid, cimetidine, non-steroidal anti-inflammatory medicines, antibiotics and oral hypoglycaemic medicines. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Additional information

Concomitant administration of 240 ml of grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers did not show a significant effect on the pharmacokinetic properties of amlodipine.

Co-administration of amlodipine with cimetidine had no significant effect on the pharmacokinetics of amlodipine.

Co-administration of amlodipine with atorvastatin, digoxin, warfarin or ciclosporin had no significant effect on the pharmacokinetics or pharmacodynamics of these agents.

ADVERSE EFFECTS

Fixed Dose Combination

The safety and tolerability of TWYNSTA has been evaluated in five controlled clinical studies with over 3500 patients, over 2500 of whom received telmisartan in combination with amlodipine.

Adverse reactions reported in clinical trials with telmisartan plus amlodipine are shown below according to system organ class.

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare

(≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations	
Rare:	Cystitis
Psychiatric disorders	
Rare:	Depression, anxiety, insomnia
Nervous system disorders	
Common:	Dizziness
Uncommon:	Somnolence, migraine, headache, paraesthesia
Rare:	Syncope, peripheral neuropathy, hypoaesthesia, dysgeusia, tremor
Ear and labyrinth disorders	
Uncommon:	Vertigo
Cardiac disorders	
Uncommon:	Bradycardia, palpitations
Vascular disorders	
Uncommon:	Hypotension, orthostatic hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Cough

Gastro-intestinal disorders	
Uncommon:	Abdominal pain, diarrhoea, nausea
Rare:	Vomiting, gingival hypertrophy, dyspepsia, dry mouth
Skin and subcutaneous tissue disorders	
Uncommon:	Pruritus
Rare:	Eczema, erythema, rash
Musculoskeletal and connective tissue disorders	
Uncommon:	Arthralgia, muscle spasms (cramps in legs), myalgia
Rare:	Back pain, pain in extremity (leg pain)
Renal and urinary disorders	
Rare:	Nocturia
Reproductive system and breast disorders	
Uncommon:	Erectile dysfunction
General disorders and administration site conditions	
Common:	Peripheral oedema
Uncommon:	Asthenia (weakness), chest pain, fatigue, oedema
Rare:	Malaise
Investigations	
Uncommon:	Hepatic enzymes increased
Rare:	Blood uric acid increased

Additional information on the combination

Peripheral oedema, a recognised dose dependent side effect of amlodipine, was generally observed at a lower incidence in patients who received the telmisartan/amlodipine combination than in those who received amlodipine alone.

The oedema related events (peripheral oedema, generalised oedema, and oedema) were consistently lower in patients who received TWYNSTA as compared to patients who received amlodipine 10 mg. In the factorial design trial, the oedema rates were 1.3% with TWYNSTA 40/5 mg and 80/5 mg, 8.8 % with TWYNSTA 40/10 mg and 80/10 mg and 18.4% with amlodipine 10 mg. In patients not controlled on amlodipine 5 mg the oedema rates were 4.4% for 40/5 mg and 80/5 mg and 24.9% for amlodipine 10 mg.

Additional information on individual components

Side effects previously reported with one of the individual components (amlodipine or telmisartan) may be potential side effects with TWYNSTA as well, even if not observed in clinical trials or during the post-marketing period.

Telmisartan

Other additional side effects reported with telmisartan monotherapy in the hypertension indication, irrespective of causal association, were as follows:

Infections and infestations: sepsis including fatal outcome, urinary tract infections (including cystitis), upper respiratory tract infections, bronchitis, infection, abcess, otitis media

Blood and lymphatic system disorders: anaemia, eosinophilia, thrombocytopenia

Immune system disorders: anaphylactic reaction, hypersensitivity, allergy

Metabolism and nutrition disorders: hyperkalaemia, hypoglycaemia (in a diabetic patients), gout, hypercholesterolaemia, diabetes mellitus

Psychiatric disorders: nervousness

Eye disorders: visual disturbance, conjunctivitis

Ear and labyrinth disorders: tinnitus, earache

Cardiac disorders: tachycardia, angina pectoris

Vascular disorders: cerebrovascular disorder

Respiratory, thoracic and mediastinal disorders: dyspnoea, asthma, epistaxis

Gastrointestinal disorders: flatulence, stomach discomfort, constipation, gastritis, haemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache

Hepatobiliary disorders: hepatic function abnormal, liver disorder*
**Most cases of hepatic function abnormal / liver disorder from post-marketing experience with telmisartan occurred in patients in Japan, who are more likely to experience these adverse reactions*

Skin and subcutaneous tissue disorders: angioedema (with fatal outcome), hyperhidrosis, urticaria, drug eruption, toxic skin eruption, dermatitis

Musculoskeletal and connective tissue disorders: tendon pain (tendinitis like symptoms), arthritis

Renal and urinary disorders: renal impairment including acute renal failure (see also PRECAUTIONS), micturition frequency

General disorders: influenza-like illness, pain, fever

Investigations: haemoglobin decreased, blood creatinine increased, blood creatine phosphokinase (CPK) increased, abnormal ECG

Amlodipine

Other additional side effects reported with amlodipine monotherapy, irrespective of causal association, were as follows:

Blood and lymphatic system disorders: leucopenia, thrombocytopenia

Immune system disorders: hypersensitivity

Metabolism and nutrition disorders: hyperglycaemia, anorexia

Psychiatric disorders: mood change, confusional state, abnormal dreams, depersonalisation, nervousness

Eye disorders: visual impairment, conjunctivitis, diplopia, eye pain

Ear and labyrinth disorders: tinnitus, vertigo

Cardiac disorders: myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation, tachycardia

Vascular disorders: vasculitis

Respiratory, thoracic and mediastinal disorders: dyspnoea, rhinitis, epistaxis

Gastrointestinal disorders: change of bowel habit, pancreatitis, gastritis, constipation, dysphagia, flatulence

Hepatobiliary disorders: hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis)

Skin and subcutaneous tissue disorders: alopecia, purpura, skin discolouration, hyperhidrosis, angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity reaction

Musculoskeletal and connective tissue disorders: arthrosis

Renal and urinary disorders: micturition disorder, pollakiuria, micturition frequency

Reproduductive system and breast disorders: gynaecomastia, sexual dysfunction (male and female)

General disorders: pain, weight increased, weight decreased

DOSAGE AND ADMINISTRATION

TWYNSTA should be taken once daily.

TWYNSTA may be taken with or without food.

TWYNSTA can be administered with other antihypertensive drugs.

Replacement therapy

Patients receiving telmisartan and amlodipine from separate tablets can instead receive TWYNSTA containing the same component doses in one tablet once daily, e.g. to enhance convenience or compliance.

Add on therapy

TWYNSTA may be administered in patients whose blood pressure is not adequately controlled with amlodipine or telmisartan alone.

Individual dose titration with the components (i.e. telmisartan and amlodipine) is recommended before changing to the fixed-dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

Patients treated with 10 mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to TWYNSTA 40/5 mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Renal impairment

No dosage adjustment is required for patients with renal impairment, including those on haemodialysis. Amlodipine and telmisartan are not dialysable. (see PRECAUTIONS)

Hepatic impairment

In patients with mild to moderate hepatic impairment, TWYNSTA should be administered with caution. For telmisartan, the dosage should not exceed 40 mg once daily. (see PRECAUTIONS)

TWYNSTA is contraindicated in patients with severe hepatic impairment. (see CONTRAINDICATIONS)

Elderly

No dose adjustment is necessary for elderly patients.

Children

TWYNSTA is not recommended for use in patients aged below 18 years due to lack of data on safety and efficacy.

OVERDOSAGE

In case of overdose, advice can be obtained from the Poisons Information Centre (telephone 13 11 26).

Symptoms

There is no experience of overdose with TWYNSTA. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects.

The most prominent manifestations of telmisartan overdosage were hypotension, tachycardia; bradycardia might also occur.

Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome may occur.

Treatment

Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Telmisartan and amlodipine are not removed by haemodialysis.

PRESENTATION AND STORAGE CONDITIONS

TWYNSTA 40/5 mg tablets are oval, biconvex shaped two layer tablets, white to off white on one side and blue on the other side. The white side is debossed with Boehringer Ingelheim company logo and ‘A1’. The blue side is plain. Each tablet contains 40 mg telmisartan and 5 mg amlodipine.

TWYNSTA 40/10 mg tablets are oval, biconvex shaped two layer tablets, white to off white on one side and blue on the other side. The white side is debossed with Boehringer Ingelheim company logo and ‘A2’. The blue side is plain. Each tablet contains 40 mg telmisartan and 10 mg amlodipine.

TWYNSTA 80/5 mg tablets are oval, biconvex shaped two layer tablets, white to off white on one side and blue on the other side. The white side is debossed with Boehringer Ingelheim company logo and ‘A3’. The blue side is plain. Each tablet contains 80 mg telmisartan and 5 mg amlodipine.

TWYNSTA 80/10 mg tablets are oval, biconvex shaped two layer tablets, white to off white on one side and blue on the other side. The white side is debossed with Boehringer Ingelheim

company logo and ‘A4’. The blue side is plain. Each tablet contains 80 mg telmisartan and 10 mg amlodipine.

TWYNSTA tablets are available in blister packs containing 7, 14, 28, 30, 56 and 98 tablets.

Not all pack sizes are being distributed in Australia.

Storage

Store below 30°C.

Store in original package in order to protect from light and moisture.

TWYNSTA tablets should not be removed from their foil pack until required for administration.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF APPROVAL

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Therapeutic Goods Administration

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