Svar på Lægemiddelstyrelsens høring over tilskudsstatus for kombinationspræparaterne indeholdende metoprolol og felodipin, verapamil og trandolapril, captopril og hydrochlorthiazid, enalapril 20 mg og hydrochlorthiazid 6 mg samt perindopril og amlodipin

Abbott
AstraZeneca
Paranova
Servier

Lægemiddelstyrelsen den 19. december 2008

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Att.: Elisabeth Thomsen

11. december 2008

Revurdering af tilskudsstatus for kombinationslægemidler i ATC-gruppe C02, C03, C07, C08 og C09, Tarka

Under henvisning til Lægemiddelstyrelsens brev af 24. november 2008 vedrørende "Revurdering af tilskudsstatus for kombinationslægemidler i ATC-gruppe C02, C03, C07, C08 og C09, Tarka fremsendes hermed indvendinger til medicintilskudsnævnets forslag om at fjerne tilskuddet til Tarka.

Abbott Laboratories A/S er af den opfattelse, at der er et klart behov for kombinationslægemidler, og at kombinationslægemidler har en plads i behandlingen af hypertension. Kombinationslægemidler er en god alternativ behandlingsmulighed, når effekten af monoterapi ikke har været tilstrækkelig. Tarka er et godt alternativ til tiazid-kombinationslægemidler, idet Tarka giver sammenlignelig reduktion i blodtrykket og samtidig giver en signifikant nedsættelse af risikoen for type II diabetes. Den forøgede kardiovaskulære risiko, som kombinationen af hypertension og diabetes udgør, medfører, at alle behandlinger, som kan reducerer blodtrykket og samtidig nedsætte risikoen for udvikling af type II diabetes, er vigtige i klinisk praksis. Abbott Laboratories A/S er derfor af den opfattelse, at tilskuddet til Tarka bør opretholdes af følgende årsager, som understøttes i vedlagte støttedokument:

- Den kliniske effekt af kombinationslægemidlet Tarka er signifikant mere effektiv end monterapi.
- Behandlingsregimer, som indeholder verapamil, har vist sig at yde en vis beskyttelse mod udvikling af type II diabetes.
- Kombinationslægemidler som Tarka understøtter, som nævnt i Lægemiddelstyrelsen brev af 24. november 2008, bedre compliance i lægemiddelanvendelsen, især for patienter, som er i behandling med mange lægemidler samtidigt.
- Patienter, som ikke har haft tilstrækkelig effekt af monoterapi, skal have mulighed for at fortsætte behandlingen af forhøjet blodtryk med et kombinationslægemiddel, som f.eks. Tarka og stadig kunne opretholde tilskud til behandlingen.

Venlig hilsen

Abbott Laboratories A/S
Ulla Kock

Abbott
A Promise for Life

"For the treatment of hypertension in patients who are not adequately controlled with trandolapril monotherapy"

SUBMISSION TO

THE DANISH MEDICINES AGENCY
Dec 2008

Submission prepared by:

Abbott Laboratories A/S

Abbott
A Promise for Life

TABLE OF CONTENTS

INTRODUCTION

TARKA® is a fixed combination of two drugs used to treat hypertension: trandolapril (an angiotensin converting enzyme inhibitor; ACEI) and verapamil (a calcium channel blocker; CCB).

1. Evidence of the additive effect of verapamil-SR to trandolapril:

   A single head-to-head study (TV-51-HTN trial; Messerli et al, 1998) comparing a trandolapril/ verapamil-SR (4/ 240) combination to the component monotherapies is presented. This study demonstrates a significant difference on all systolic and diastolic blood pressure (BP) endpoints when the combination is compared to the monotherapies and shows that there is clear "additive beneficial effectiveness of the components" when provided as a combination. As noted in the Public Summary Document (PSD), "a 2 mmHg margin is considered the minimum clinically acceptable difference in diastolic BP (DBP)". The results of the head-to-head study show that both 240 mg verapamil-SR and 4 mg trandolapril as monotherapy provide a clinically acceptable difference in blood pressure over placebo (4.3 and 4.5 mmHg reductions respectively). Furthermore, the magnitude of the difference in DBP between the combination of 240 mg verapamil-SR with 4 mg trandolapril and either of the monotherapies is also a clinically acceptable difference (approximately 3.8 and 3.6 mmHg respectively). Similar results are seen when the systolic blood pressure (SBP) results are examined.

2. The clinical need of such a combination and possible inappropriate replacement of ACEI/thiazide combinations:

   There is growing evidence that the use of 'newer' antihypertensives (such as ACEIs, AIIRAs and CCBs) results in a lower rate of new-onset diabetes than the use of 'older' antihypertensives (diuretics and beta-blockers). A recent publication by Taylor et al (2006) examined the association between different classes of anti-hypertensive medications and the risk of incident type 2 diabetes. The study found that after controlling for a number of factors the relative risk of incident diabetes in patients taking a thiazide diuretic was 1.20 (95%CI 1.08-1.33) in older women and 1.45 (1.17-1.79) in younger women, and 1.36 in men (1.17-1.58). The risk taking a beta-blocker compared to not taking one was 1.32 (1.20-1.46) in older women and 1.20 (1.05-1.38) in men. ACE inhibitors and calcium channel blockers were not associated with increased risk. Similarly, in an analysis by Mancia et al (2006), the absolute reduction in new-onset diabetes for newer treatments compared with older treatments across

14 trials ranged from 0.8 to 7.1/1000 py, with the mean absolute change being –5.61 ± 2.32 (SEM) per 1000 py.

Furthermore, two recent studies have shown that a verapamil-containing regimen may confer some protection against the development of new-onset type II diabetes when compared with 'older' regimens. In the INVEST study, which was conducted in subjects with hypertension and documented coronary artery disease, the incidence of new-onset diabetes was significantly lower with a verapamil-based regimen compared with an atenolol-based regimen (7.0% vs. 8.2%; RR 0.85; 95% CI 0.77, 0.95; Pepine et al, 2003). Most recently, the Study of Trandolapril/ verapamil-SR and Insulin Resistance (STAR) examined the glucose tolerance and diabetes onset in a group of subjects with metabolic syndrome. The study compared an ACEI/ verapamil-SR combination (TARKA®) to an angiotensin II receptor antagonist (AIIRA)/ hydrochlorothiazide (HCTZ) combination (HYZAAR). Two-hour post-prandial glucose levels were lowered 3.8 mg/dL in the TARKA® arm and increased 26.0 mg/dL in the HYZAAR arm. New onset diabetes (defined as a fasting blood glucose of ≥ 126 mg/dL and/or 2 hr OGTT of ≥ 200 mg/dL) was almost three times greater in the HYZAAR arm (27%) compared with the TARKA® arm (11.5%) at study end, an absolute reduction of 15.5% when TARKA® is compared to HYZAAR. These results strongly suggest that a combination of verapamil-SR and trandolapril is more suitable for the treatment of hypertension in subjects with metabolic syndrome, than a combination of HCTZ and losartan.

3. Summary:

There is a clear clinical need for a combination product such as TARKA® . Based on a review of International CPGs, a CCB/ACEI combination is an accepted member of the possible range of treatments for hypertension. Its particular place in hypertension therapy appears to be as an option for second-line therapy after failure of appropriate monotherapy.

TARKA® provides an alternative to thiazide combinations because it provides similar improvement in blood pressure, but results in significantly lower rates of new-onset diabetes, as shown by the STAR study. Given the increased cardiovascular risk that a combination of diabetes with hypertension confers, any treatment that can lower blood pressure, while not increasing the risk of developing diabetes, has an important role in clinical practice.

Clinical evidence

SOURCES OF CLINICAL EVIDENCE:

A literature search identified three studies that were relevant to this submission. A head-to-head study examining trandolapril 4mg, verapamil-SR 240mg and the combination of trandolapril and verapamil (4/240). This study, TV-51-HTN, is used as the pivotal evidence in this submission. Two supportive studies are provided, a bioequivalence study (TV-4-CP) and STAR, a study comparing TARKA and HYZAAR. The bioequivalence study is not presented in detail but is provided as a reference to support the bioequivalence between the individual components of trandolapril 4mg and verapamil-SR 240mg given concomitantly are bioequivalent to TARKA® 4/240.

CLINICAL EVIDENCE

TV-51-HTN was a US, multicentre, randomised, double blind study with a parallel design and was conducted in adult patients who had mild to moderate essential hypertension. In TV-51-HTN patients were mainly Caucasian with essential hypertension for 8- 9 years, they were initiated on a combination of 4mg trandolapril and 120mg of verapamil-SR, this was titrated to 4mg/ 240mg verapamil-SR in the second week of the double blind period (week 6) of the study. All patients were evaluable and analysed using an ITT analysis. The trial population should reasonably reflect the PBS population where listing is sought.

STAR was a prospective, randomised, open-label study with blinded outcome evaluation. STAR enrolled patients older than 21 years with the presence of the metabolic syndrome. Therapy was initiated using either the 2 mg trandolapril/ 180mg verapamil combination (TARKA®) or the 50mg losartan/ 12.5 hydrochlorothiazide combination (HYZAAR). The study included scheduled up titration at weeks 4 and 8. At the end of the study 91/119 (76.5%) of patients in the T/V arm and 89/121 of patients (73.6%) in the L/H arm were up-titrated to 4/240mg T/V and 100/25mg L/H, respectively. The analysis was conducted using an ITT analysis. The results of STAR should reasonably reflect an Australian population with the same characteristics.

CLINICAL RESULTS

Study TV-51-HTN measured efficacy as the change in blood pressure from baseline to end point and the rate of response. Response was defined as a diastolic blood pressure of less than 90mmHg and/ or a decrease in blood pressure of ≥10mmHg.

Diastolic Blood Pressure: Between treatment comparisons at endpoint- Trough

The results for sitting, supine and standing diastolic BP are summarised in **Figure ES1**. For the primary endpoint of sitting diastolic BP all active treatments groups had statistically significant ($p<0.01$) lower endpoint mean trough sitting diastolic BP compared to placebo (see **Fig.ES1**). At endpoint, the combination therapy had statistically significant ($p<0.01$) lower mean trough sitting diastolic BP compared to its monotherapies. The combination provided a further -3.6 mmHg reduction in BP versus trandolapril and a further -3.8 mmHg reduction compared to verapamil-SR.

The between-treatment comparisons for supine and standing at endpoint were similar to sitting BP with all treatment groups having statistically significant ($p<0.01$) lower mean trough supine and standing diastolic BP compared to placebo (see **Fig.ES1**). The combination therapy had statistically significant ($p<0.01$) lower mean trough supine and standing diastolic BP at endpoint compared to its monotherapies. The combination provided a further -4.2 (supine) and -3.6 mmHg (standing) reduction in BP versus trandolapril and a further -3.6 (supine) and -3.7 mmHg (standing) reduction compared to verapamil-SR.

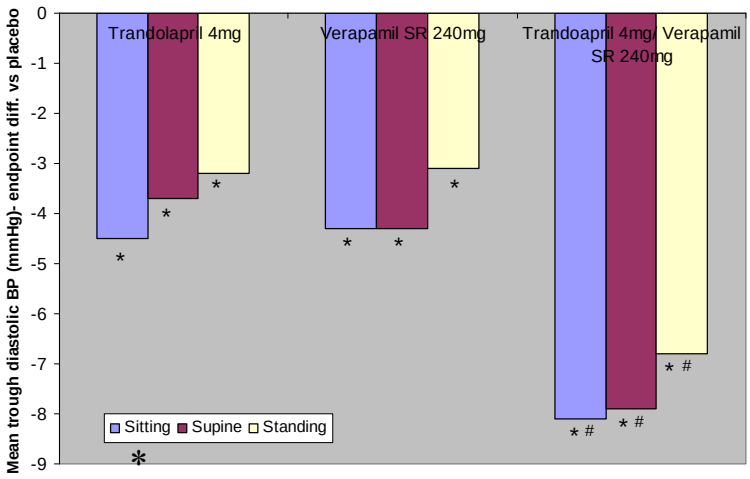


Figure ES1: Mean sitting, supine and standing trough diastolic BP (mmHg)-Between treatment comparisons at endpoint vs. placebo. (*P<0.01 treatment versus placebo; # p<0.01 monotherapies versus combination)

A summary of the comparative changes in diastolic and systolic BP from baseline to endpoint for TV-51-HTN are summarised in Table **ES1**. The results of the head-to-head study show

that both 240 mg verapamil-SR and 4 mg trandolapril as monotherapy provide a statistically significant and clinically acceptable difference in blood pressure over placebo across all systolic and diastolic blood pressure (BP) endpoints when the combination is compared to the monotherapies and shows that there is clear "additive beneficial effectiveness of the components" when given in combination.

Supportive Trials

The result for the percentage of patients with new onset diabetes is presented in **Figure ES2**. At study end, 27% of patients on HYZAAR had new onset diabetes compared to 11.5% on

Table ES1: Baseline-Endpoint Changes in Blood pressure for pivotal clinical study TV-51-HTN

Blood Pressure	Treatment	Comparison	Comparative difference in BP from baseline in mmHg						P value
			Diastolic			Systolic			
			Sitting	Supine	Standing	Sitting	Supine	Standing	
Trough	Trandolapril 4mg	Placebo	**-4.5**	**-3.7**	**-3.2**	**-9.0**	**-7.1**	**-8.8**	**All p<0.01**
	Verapamil SR 240mg	Placebo	**-4.3**	**-4.3**	**-3.1**	**-8.0**	**-5.6**	**-5.9**	**All p<0.01**
	Trandoapril 4mg/ verapamil-SR 240	Placebo	**-8.1**	**-7.9**	**-6.8**	**-12.9**	**-12.1**	**-11.5**	**All p<0.01**
	Trandoapril 4mg/ verapamil-SR 240	Trandolapril 4mg	**-3.6**	**-4.2**	**-3.6**	**-3.9**	**-5.0**	**-2.7**	**P<0.01 or P<0.05**
	Trandoapril 4mg/ verapamil-SR 240	Verapamil -SR 240 mg	**-3.8**	**-3.6**	**-3.7**	**-4.9**	**-7.5**	**-5.6**	**All p<0.01**
Peak	Trandolapril 4mg	Placebo	**-6.0**	**-5.1**	**-6.1**	**-11.5**	**-11.5**	**-13.0**	**All p<0.01**
	Verapamil SR 240mg	Placebo	**-9.1**	**-7.3**	**-8.5**	**-12.5**	**-12.4**	**-13.0**	**All p<0.01**
	Trandoapril 4mg/ verapamil-SR 240	Placebo	**-12.4**	**-11.9**	**-12.9**	**-20.3**	**-19.5**	**-21.0**	**All p<0.01**
	Trandoapril 4mg/ verapamil-SR 240	Trandolapril 4mg	**-6.4**	**-6.8**	**-6.8**	**-8.8**	**-8.0**	**-8.0**	**All p<0.01**
	Trandoapril 4mg/ verapamil-SR 240	Verapamil -SR 240 mg	**-3.3**	**-4.6**	**-4.4**	**-7.8**	**-7.1**	**-8.0**	**All p<0.01**

TARKA®, an absolute reduction of 15.5% when TARKA® is compared to HYZAAR. This difference was significant ($p<0.01$). A similar significant difference between treatments was observed by week 12 of the 52-week study (see **Fig.ES2**).

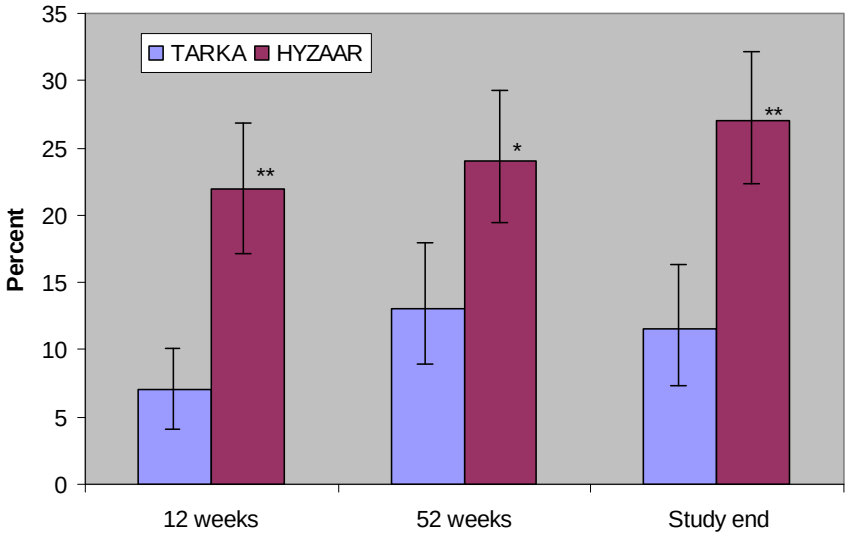


Figure ES2: New onset of diabetes (FBG ≥ 126 mg/dL; * p≤0.05 and **p≤0.01 between treatment groups)

INTEPREPRETATION OF THE CLINAL EVIDENCE

Based on the results of TV-51HTN the category that best describes TARKA® is:

(i) The combination is significantly more effective than the individual components given as monotherapy and is no worse for efficacy and safety than the individual components given concomitantly.

Clinical need

The relationship between hypertension and cardiovascular risk

Cardiovascular risk can be determined based on the severity of hypertension; however, risk levels may be modified in the presence of other risk factors. Other risk factors associated with increased cardiovascular risk include, but are not limited to, increased age, smoking status, obesity and diabetes. As shown in **Table 1**, cardiovascular risk is increased when both high blood pressure and other risk factors are present. For example, mild hypertension alone is associated with a low cardiovascular risk, while mild hypertension in the presence of diabetes results in a high cardiovascular risk.

Table 1 Total cardiovascular risk in the presence of various risk factors

Other risk factors and disease history	Mild hypertension	Moderate hypertension	Severe hypertension
No other risk factors	Low risk	Medium risk	High risk
1 or 2 risk factors but not diabetes	Medium risk	Medium risk	Very high risk
3 or more risk factors or target organ damage or diabetes mellitus	High risk	High risk	Very high risk
Associated clinical conditions	Very high risk	Very high risk	Very high risk

Adapted from J Hypertens 1999; 17(2): 151-183.

Treatment of hypertension

There are a number of different classes of drug treatment available for hypertension. These include thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors (ACEIs), angiotensin II converting enzyme inhibitors (AIIRAs) and calcium channel blockers (CCBs). **Table 2** shows the main characteristics of the drug classes used to treat hypertension.

Table 2 Main characteristics of classes of drugs used to treat hypertension[a]

Class	Examples[b]	Mode of action	Notes
Thiazide diuretics	Bendrofluazide Chlorthalidone Hydrochloro-thiazide Indapamide	Vasodilation and moderate diuresis	Low-dose thiazide-type diuretics produce (near) maximal BP lowering. Higher doses can cause side effects. Generally well tolerated. Potassium changes in the blood can be corrected once identified.
Beta-blockers	Atenolol Metoprolol	Blocking beta-receptors in the heart slows down and decreases the force of contraction of the heart	Contraindicated with asthma, heart-block or a non-DHP CCB. Cautions apply to patients with diabetes or peripheral vascular disease. Reported side effects include lethargy, depression and sleep disturbance.
ACEIs	Captopril Enalapril Fosinopril Lisinopril Perindopril Quinapril Ramipril Trandolapril	Prevent conversion of the protein Angiotensin I to Angiotensin II which raises blood pressure	Dose titration and monitoring necessary. Contraindicated in pregnancy and some kidney diseases. Caution when initiating on a diuretic or with renal failure. Adverse effects include a persistent dry cough, rash and loss of taste.
AIIRAs	Candesartan Eprosartan Irbesartan Losartan Telmisartan	Blocks the action of Angiotensin II by directly clocking the receptor site.	Contraindications and side effect profile similar to ACEIs but no dry cough.
CCBs	<u>DHP</u> Amlodipine Felodipine Lercanidipine Nifedipine	Reduced flow of calcium to vascular smooth muscle, reducing contraction efficiency and relaxing the vasculature.	Reported side effects include initial headaches, palpitations and facial flushing; ankle swelling
	<u>Non-DHP</u> Ditiazem Verapamil	Additionally affect the conduction system, slowing heart rate	Caution against use in heart failure or use with a beta-blocker. Reported side effects include constipation (verapamil) and skin rashes (dilitiazem).

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; AIIRAs, angiotensin II receptor antagonists; BP, blood pressure; CCBs, calcium channel blockers; DHP, dihydropyridine.

[a] Table modified from CHSR (2004) (Table 16, p106).

[b] Heart Foundation (2004).

Thiazide diuretics are often recommended for the first-line treatment of uncomplicated hypertension, due to their similar efficacy to other antihypertensive agents and lower cost, although other classes can be substituted or added for second-line therapy. Examples of treatment algorithms for uncomplicated hypertension are shown in **Table 3**.

Table 3 Treatment algorithms for hypertension in three recent hypertension clinical practice guidelines

	Hypertension
CHEP (2006)	Step 1 Initial therapy should be monotherapy (thiazide diuretics, beta-blockers, ACEIs, AIIRAs or long-acting CCBs) Step 2 If target blood pressure levels are not reached, then add on from first-line treatments
BHS (2004)	Step 1 (initial monotherapy): ACEI/ARB or beta-blocker in younger and non-black patients or CCBs or thiazides in older or black patients Step 2 (failure to lower to required levels): ACEI/ARB or beta-blocker (but be careful of potential to induce diabetes) and CCB or thiazide Step 3 (failure to lower BP to required levels): ACEI/ARD and CCB and thiazide Step 4 (resistant hypertension): add either alpha-blocker or spironolactone or other diuretic.
NICE (2004)	Step 1 Start with a thiazide-like diuretic Step 2 If not tolerated change to, or if not controlled add (i) a beta-blocker if the risk of new-onset diabetes is low; or (ii) an ACEI if the risk on new-onset diabetes is high. Step 3 If not tolerated change to, or if not controlled add, a CCB. Use only DHP CCBs if adding to a beta-blocker Step 4 If not responding consider another drug or referral.

Abbreviations: BHS, British Hypertension Society; CHEP, Canadian Hypertension Education Program; NICE, National Institute for Clinical Excellence.

As hypertension is one of a number of many risk factors for cardiovascular disease, the choice of treatment is often influenced by the presence of other risk factors, pre-existing vascular disease and associated conditions such as diabetes. The most recent of the hypertension CPGs, published by the Canadian Hypertension Education Program (CHEP, 2006), provides guidance for the first- and second-line treatment of hypertension in the presence of other comorbidities, as shown in **Table 4**. This has been used as an example only and it is important to note that are some variations in the treatment recommendations made by different CPGs, most probably due to the differences in the studies assessed and local treatment practice.

Table 4 Treatment of hypertension with/without compelling indications (CHEP, 2006)

Risk factor/disease	First-line therapy	Second-line therapy	Cautions
Isolated systolic hypertension without compelling indications for specific agents	Thiazide diuretics, AIIRAs or long-acting DHP CCBs	Combination of first-line drugs	
Diabetes mellitus with nephropathy	ACEIs or AIIRAs	Addition of one or more of thiazide diuretics, cardio-selective beta-blockers, long-acting CCBs or use of an ACEI/AIIRA combination	
Diabetes mellitus without nephropathy	ACEIs, AIIRAs or thiazide diuretics	Combination of first-line drugs or addition of cardio-selective beta-blockers or long-acting CCBs	
Angina	Beta-blockers and ACEIs	Long-acting CCBs	
Established atherosclerotic disease and peripheral arterial disease	ACEIs added to other therapy		For severe peripheral arterial disease avoid beta-blockers
Prior myocardial infarction	Beta-blockers and ACEIs	Combination of additional agents	
Heart failure	ACEIs (AIIRAs if intolerant), beta-blockers and spironolactone	AIIRAs or hydralazine/isosorbide dinitrate; thiazide or loop diuretics, as additive therapy	Avoid non-DHP CCBs (dilitiazem, verapamil)
Stroke or transient ischemic attack	ACEI/diuretic combination		
Chronic kidney disease	ACEIs (diuretics as additive therapy)	Combination of additional agents (AIIRAs if ACEI intolerant)	Avoid ACEIs if bilateral renal artery stenosis
Left ventricular hypertrophy	ACEIs, AIIRAs, long-acting CCBs, thiazide diuretics (beta-blockers for those < 60)		Avoid hydralazine and minoxidol

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; AIIRA, angiotensin II receptor antagonists; CCBs, calcium channel blockers; DHP, dihydropyridine.

Calcium channel blockers

CCBs are a structurally and functionally heterogeneous group of medications that are used widely to control blood pressure and manage symptoms of angina. There are two main subclasses of CCBs: dihydropyridines (DHPs), including amlodipine, felodipine, nicardipine and nifedipine, and non-DHPs, including dilitiazem and verapamil. CCBs can be short or long-acting, although it should be noted that short-acting CCBs are not recommended for use in the treatment of hypertension. Examples of long-acting CCBs include amlodipine, nifedipine gastrointestinal therapeutic system and extended-release verapamil.

All CCBs act to lower arterial pressure by (i) reducing peripheral vascular resistance and (ii) improving myocardial oxygen supply by vasodilating coronary arteries (Eisenberg et al, 2004). Differences between the actions of different subclasses of CCBs occur because different agents bind at different calcium channel types. Some of the differential effects of subclasses of CCBs are shown in **Table 5**. DHP CCBs are more selective at blocking L-type calcium channels in vascular smooth muscle cells, thereby inducing vascular relaxation with a fall in vascular resistance and arterial pressure. Non-DHPs reduce heart rate and myocardial contractility, thereby reducing oxygen demand. Verapamil has an additional antiarrhythmic action through its effects on the AV node.

Table 5 Differential effects of different subclasses and examples of CCBs (Eisenberg et al, 2004)

Effect	Dihydropyridines		Non-dihydropyridines	
	Amlodipine	**Nifedipine**	**Diltiazem**	**Verapamil**
Heart rate	↑/0	↓	↓	↓
SA node conduction	0	0	↓↓	↓
AV node conduction	0	0	↓	↓
Myocardial contractility	↓/0	↓/0	↓	↓↓
Neurohormonal activation	↑/0	↑	↑	↑
Vascular dilatation	↑↑	↑↑	↑	↑
Coronary flow	↑	↑	↑	↑

Adverse effects of CCBs

The differing mechanisms of action of the two subclasses of CCBs also results in slightly different side effect profiles. Side effects associated with DHP CCBs include (i) dose-

dependant peripheral oedema and (ii) gum hypertrophy (Williams et al, 2004). Side effects associated with non-DHP CCBs include: (i) peripheral oedema (although less than DHP CCBs), (ii) they are negatively ionotropic and chronotropic and therefore should be avoided in patients with compromised LVF and used with extreme caution in combination with beta-blockers; and (iii) verapamil is associated with causing constipation (Williams et al, 2004).

The results of early studies conducted in hypertensive patients with no known coronary artery disease suggested an association between CCBs and cardiovascular adverse events, such as a 58% increase in the risk of MI for CCBs compared with diuretics (Psaty et al, 1995). Furberg and Psaty (1996) subsequently concluded that CCBs should not be used for the first-line treatment of hypertension. However, other studies did not show this association and it was suggested that the increased risk was only present with short-acting formulations of CCBs. **The results of recent large clinical trials suggest that CCBs are <u>not</u> associated with an increased risk of cardiovascular events** (as shown in **Table 6** and **Figure 1**), particularly in the non-DHP CCB and long-acting CCB groups to which the form of verapamil (verapamil-SR) used in TARKA® belong.

Table 6 Risk of occurrence of major cardiovascular events[a] with CCBs compared with other antihypertensive agents (Eisenberg et al, 2004)

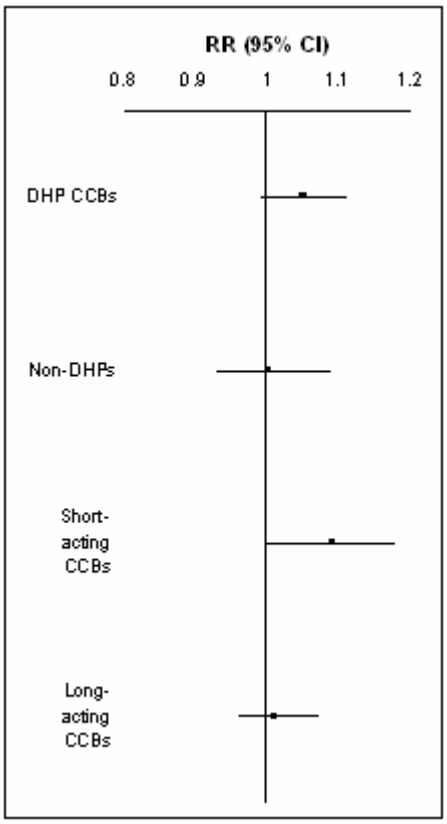
CCB group	CCBs n/N (%)	Other antihypertensive agents n/N (%)	RR (95% CI)
DHP CCBs			
ALLHAT	1466/9048 (16.2)	2451/15,255 (16.1)	1.00 (0.94, 1.07)
STOP-2	636/2196 (28.9)	1223/4418 (27.7)	1.07 (0.95, 1.19)
INSIGHT	200/3157 (6.3)	182/3164 (5.7)	1.11 (0.90, 1.36)
MIDAS	17/442 (3.8)	11/441 (2.5)	1.56 (0.72, 3.38)
ABCD	47/235 (20.0)	29/235 (12.3)	1.78 (1.07 , 2.94)
NICS-EH	9/215 (4.2)	13/214 (6.1)	0.68 (0.28, 1.62)
FACET	23/191 (12)	14/189 (7.4)	1.71 (0.85, 3.44)
CASTEL	32/146 (21.9)	26/205 (12.7)	1.93 (1.09, 3.41)
TOTAL	*2430/15,630 (15.5)*	*3949/24,121 (16.4)*	*1.05 (0.99, 1.11)*
Non –DHP CCBs			
INVEST[b]	514/11,267 (4.6)	534/11,309 (4.7)	0.98 (0.90, 1.06)
CONVINCE[b]	264/8241 (4.5)	365/8361 (4.4)	1.02 (0.88, 1.18)
NORDIL	466/5410 (8.6)	453/5471 (8.3)	1.04 (0.91, 1.20)
VHAS[b]	15/707 (2.1)	13/707 (1.8)	1.16 (0.55, 2.45)
TOTAL	*1359/25,625 (5.3)*	*1365/25,848 (5.3)*	*1.00 (0.93, 1.09)*
Short-acting CCBs			
NORDIL	466/5410 (8.6)	453/5471 (8.3)	1.04 (0.91, 1.20)
STOP-2	636/2196 (28.9)	1223/4418 (27.7)	1.07 (0.95, 1.19)
VHAS[b]	15/707 (2.1)	13/707 (1.8)	1.16 (0.55, 2.45)
MIDAS	17/442 (3.8)	11/441 (2.5)	1.56 (0.72, 3.38)
ABCD	47/235 (20)	29/235 (12.3)	1.78 (1.07, 2.94)
NICS-EH	9/215 (4.2)	13/214 (6.1)	0.68 (0.28, 1.62)
CASTEL	32/146 (21.9)	26/205 (12.7)	1.93 (1.09, 3.41)
TOTAL	*1222/9351 (13.1)*	*1768/11,691 (15.1)*	*1.09 (1.00, 1.18)*
Long-acting CCBs			
ALLHAT	1466/9048 (16.2)	2451/15,255 (16.1)	1.00 (0.94, 1.07)
INVEST[b]	514/11,267 (4.6)	534/11,309 (4.7)	0.98 (0.90, 1.06)
CONVINCE[b]	364/8241 (4.4)	365/8361 (4.4)	1.02 (0.88, 1.18)
INSIGHT	200/3157 (6.3)	182/3164 (5.8)	1.11 (0.90, 1.36)
FACET	23/191 (12.0)	14/189 (7.4)	1.71 (0.85, 3.44)
TOTAL	*2567/31,904 (8)*	*3546/38,278 (9.3)*	*1.01 (0.96, 1.07)*

Abbreviations: ABCD, appropriate Blood Pressure Control in Diabetes; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CASTEL, Cardiovascular Study in the Elderly; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular Endpoints; FACET, Fosinopril versus Amlodipine Cardiovascular Events Trial; INSIGHT, International Nifedipine Gastrointestinal Therapeutic System study – Intervention as a Goal in Hypertension Treatment; INVEST, International Verapamil Slow-Release/Trandolapril Study; MIDAS, Multicentre Isradipine Diuretic Atherosclerosis Study; NICS-EH, National Intervention Cooperative Study in Elderly Hypertensives; NORDIL, Nordic Dilitiazem; STOP, Swedish Trial in Old Patients with Hypertension; VHAS, Verapamil in Hypertension and Atherosclerosis Study.

[a] Major cardiovascular events included myocardial infarction, heart failure, stroke and cardiovascular mortality, except in: (i) ALLHAT, where events included death from coronary heart disease, non-fatal myocardial infarction, coronary revascularisation procedures, and angina requiring hospitalisation; and (ii) INVEST, where the primary outcome was cardiovascular mortality.

[b] Trials assessing verapamil. It should be noted that the VHAS trial assessed a short-acting form of verapamil, while TARKA® uses a long-acting form.

Figure 1 **Risk of occurrence of cardiovascular events with CCBs compared with other antihypertensive agents**



Some studies have suggested that CCBs, especially the DHPs, are associated with an increased risk of cancer, GI bleeding and all-cause mortality. The CONVINCE study (Black et al, 2003) showed that verapamil-SR was not associated with a greater risk of new cancer or death from cancer compared with an atenolol/HCTZ combination (*P*=0.15 and 0.23 respectively). While hospitalisation due to non-intracranial bleeding was higher in the verapamil arm compared with the atenolol/HCTZ arm (1.4% vs 1.0%; *P*=0.003), there was no difference between the two arms in mortality due to intracranial bleeding (0.1% for both; *P*=0.97).

Role of CCBs in the treatment of hypertension

According to hypertension CPGs, the use of CCBs is particularly appropriate in certain groups of patients, and contraindicated in others. For example, there is strong evidence that verapamil should not be used in patients with heart failure, or in combination with beta-blockers, as noted in most clinical practice guidelines. A review of how CCBs are

recommended for use in hypertension CPGs is summarised in **Table 7**. Of relevance to this submission, the patient group for whom CCBs and CCB/ACEI combinations are most often recommended are those with, or at risk of, diabetes.

Table 7 Recommendations for use of CCBs in the treatment of hypertension in Clinical Practice Guidelines

Year	Guideline Group (Country)	CCBs (specific indications)	ACEIs + CCBs (specific indications)	Non-DHP CCBs (specific indications)
2006	CHEP (Canada)	✓	✓(diabetes/albuminuria)	
2006	ICSI (US)	✓ (diabetes, high coronary risk)		
2005	MOH (Singapore)	✓(angina, isolated systolic hypertension, diabetes mellitus)	✓(obesity, metabolic syndrome)	
2005	VA/DoD (US)	✓(Diabetes mellitus)		✓(chronic kidney disease, post-MI)
2004	BHS (UK)	✓	✓(diabetes/diabetic nephropathy)	
2004	HF (Australia)	✓(angina)	✓(diabetes/lipid abnormalities)	
2004	NICE (UK)	✓		
2004	MJA (Australia)	✓(diabetes)	✓(renal disease)	
2003	ACP (US)	✓(diabetes)		
2003	ESH-ESC (Europe)			✓(angina, carotid atherosclerosis, SV tachycardia)
2003	UMHS (US)			✓(hypertrophic cardiomyopathy, SV tachycardia, vascular headaches)
2003	JNC VII (US)	✓ (high coronary disease)		

Abbreviations: ACP, American College of Physicians; BHS, British Hypertension Society; CHEP, Canadian Hypertension Education Program; DoD, Department of Defence; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HF, Heart Foundation; ICSI, Institute for Clinical Systems Improvement; JNC VII, Seventh Report of The Joint National Committee on Prevention, Detection, Evaluation and Treatment Of High Blood Pressure; MJA, Medical Journal of Australia; MOH, Ministry of Health; NICE, National Institute for Clinical Excellence; SV, supraventricular; UMHS, University of Michigan Health System; VA, Veteran's Affairs; WHO, World Health Organisation.

There is growing evidence that the use of 'newer' anti-hypertensive agents (such as ACEIs, AIIRAs and CCBs) results in a lower rate of new-onset diabetes than the use of 'older' anti-hypertensives (diuretics and beta-blockers). A recent publication by Taylor et al (2006) examined the association between different classes of anti-hypertensive medications and the risk of incident type 2 diabetes. The study found that after controlling for a number of factors the relative risk of incident diabetes in patients taking a thiazide diuretic was 1.20 (95%CI 1.08-1.33) in older women and 1.45 (1.17-1.79) in younger women, and 1.36 in men (1.17-1.58). The risk taking a beta-blocker compared to not taking one was 1.32 (1.20-1.46) in older women and 1.20 (1.05-1.38) in men. ACE inhibitors and calcium channel blockers were not associated with increased risk. Similarly, in an analysis presented by Mancia et al (2006), the

absolute reduction in new-onset diabetes for newer treatments compared with older treatments across 14 trials ranged from 0.8 to 7.1/1000 py, with the mean absolute change being –5.61 ± 2.32 (SEM) per 1000 py. Given the additional cardiovascular risk associated with hypertension in combination with diabetes, it is important that treatments which may increase the chance of individuals developing diabetes are avoided.

More specifically, two recent studies have shown that a verapamil-containing regimen may confer some protection against the development of new-onset type II diabetes when compared with 'older' regimens. In the INVEST study, which was conducted in subjects with hypertension and documented coronary artery disease, the incidence of new-onset diabetes was significantly lower with a verapamil-based regimen compared with an atenolol-based regimen (7.0% vs 8.2%; RR 0.85; 95% CI 0.77, 0.95; Pepine et al, 2003). Most recently, STAR examined the glucose tolerance and diabetes onset in a group of subjects with metabolic syndrome. Subjects were randomised to either TARKA® (verapamil/trandolapril) or HYZAAR® (losartan/HCTZ). The higher dose (ie V240/T4 for TARKA® and L100/ 25H for HYZAAR) was received by 77% of the TARKA® group and 74% of the HYZAAR group. The primary outcome was a 2 hour oral glucose tolerance test (2hr OGTT). This was chosen because it is considered the gold standard for establishing a diagnosis of diabetes according to the American Diabetes Association.

A summary of the results of the STAR study are presented in **Table 8**. Two-hour post-prandial glucose levels were lowered 3.8 mg/dL in the TARKA® arm and increased 26.0 mg/dL in the HYZAAR arm. New onset diabetes (defined as a fasting blood glucose of ≥ 126 mg/dL and/or 2 hr OGTT of ≥ 200 mg/dL) was more than three times greater in the HYZAAR arm compared with the TARKA® arm at 12 weeks. Similar differences were seen at week 52 and study end.

Table 8 Results of the STAR study: TARKA® vs HYZAAR

Outcomes	TARKA®		HYZAAR		Change fro baseline P value
	Baseline Mean ± SD	**Endpoint Mean ± SD**	**Baseline Mean ± SD**	**Endpoint Mean ± SD**	
Primary outcome					
2 hr OGTT (mg/dL)	144 ± 44	139 ± 54	142 ± 45	168 ± 81	<0.001
Secondary outcomes					
2 hr insulin (UIU/mL)	112 ± 66	106 ± 76	106 ± 74	119 ± 83	0.025
HbA1c (%)	5.8 ± 0.6	5.9 ± 0.6	5.7 ± 0.5	6.2 ± 1.4	0.027
SBP (mmHg)	145 ± 15	131 ± 16	147 ± 17	129 ± 14	0.179
DBP (mmHg)	86 ± 10	79 ± 10	88 ± 9	79 ± 9	0.605
Pulse (bpm)	71 ± 9	72 ± 10	70 ± 11	72 ± 11	0.457

These results strongly suggest that a combination of verapamil and trandolapril is more suitable for the treatment of hypertension in subjects with metabolic syndrome, than a combination of losartan and HCTZ.

Summary

There is a clear clinical need for a combination product such as TARKA®. Based on a review of International CPGs, a CCB/ACEI combination is an accepted member of the possible range of treatments for hypertension. Listing is sought in patients who are maximally titrated on trandolapril monotherapy, which is recognised as a first line treatment option for patients with hypertension. TARKA® provides an alternative to thiazide combinations because it provides similar improvements in blood pressure, but also results in significantly lower rates of new-onset diabetes, as shown STAR. Given the increased cardiovascular risk that a combination of diabetes with hypertension confers, any treatment that can lower blood pressure, while not increasing the risk of developing diabetes, has an important role in clinical practice.

1. DETAILS OF THE PROPOSED DRUG AND ITS PROPOSED USE

Summary

TARKA® is a combination therapy of slow release verapamil hydrochloride (verapamil-SR) and trandolapril. Verapamil-SR acts to reduce arterial pressure by reducing peripheral vascular resistance through inhibition of the influx of calcium ions to smooth muscle and to contractile cells in the heart. Trandolapril is an ACEI thereby reducing vasopressor activity and contributing to peripheral vasodilation.

The proposed indication for PBS listing is: *"Hypertension in patients who are not adequately controlled on 4 mg trandolapril monotherapy."* The recommended daily dosing of TARKA® is one tablet (4/240mg) daily. Both verapamil-SR and trandolapril are generally well tolerated, with constipation, being the most common adverse event from verapamil-SR, and asthenia and malaise from trandolapril.

The main comparator(s) for TARKA® are the monotherapy agents which make up the combination.

Contraindications and precautions for TARKA® are the same as the 'cumulative' contraindications and precautions of verapamil-SR and trandolapril. The main difference between TARKA® and verapamil-SR and trandolapril given as monotherapy agents to treat hypertension is that the use of TARKA® will require the administration of a single tablet daily as opposed to one tablet of each monotherapy agent daily.

2 DATA FROM COMPARATIVE RANDOMISED TRIALS FOR THE MAIN INDICATION

Summary

Clinical evidence relating to this submission was gathered using a search of a number of databases (EMBASE, MEDLINE and the Cochrane Library) as well as a search of the TARKA® TGA registration dossier.

In total, 441 non-duplicate citations were identified by the literature search. Exclusion criteria were applied to the 441 identified citations and after the exclusion criteria were applied, four citations remained. Three studies (four citations) were identified which were considered relevant to this submission.

TV-51-HTN is used as pivotal evidence of the comparative efficacy of the combination and monotherapies. The Study of Trandolapril/ verapamil-SR and Insulin Resistance (STAR) will be used as supportive evidence. The bioequivalence study (TV-4-CP) is not presented in detail but is provided as a reference in this submission to support the bioequivalence between the individual components of trandolapril 4mg and verapamil-SR 240mg given concomitantly are bioequivalent to TARKA® 4/240.

TV-51-HTN was a US, multicentre, randomised, double blind study with a parallel design and was conducted in adult patients who had mild to moderate essential hypertension. STAR was a prospective, randomised, open-label study with blinded outcome evaluation. STAR enrolled patients older than 21 years with the presence of the metabolic syndrome.

In TV-51-HTN patients were mainly Caucasian with essential hypertension for 8- 9 years. They should be a population that reasonably reflects the PBS population where listing is sought. Similarly STAR enrolled patients with metabolic syndrome and therefore should reflect an Australian population with the same characteristics.

2.1 Description of search strategies

Clinical evidence relating to this submission was gathered using a search of a number of databases (EMBASE, MEDLINE and the Cochrane Library) as well as a search of the TARKA® TGA registration dossier. The details of the literature search are summarised in **Table 10**, **Table11** and **Table 12**.

Table 10 **Literature search: EMBASE.com**

Date	Search string	Results
15/05/2006	**#1** ('trandolapril'/exp OR 'trandolapril') AND ('verapamil'/exp OR 'verapamil')	522
	#2 ('trandolapril plus verapamil'/exp OR 'trandolapril plus verapamil') OI ('verapamil plus trandolapril'/exp OR 'verapamil plus trandolapril') OR ('tarka'/exp OR 'tarka') OR ('udramil'/exp OR 'udramil') OR ('veratran' OR 'veratran') OR ('ziaxel'/exp OR 'ziaxel')	201
	#3 #1 OR # 2	592
	#4 'hypertension'/exp OR 'hypertension'	347, 215
	#5 #3 AND #4	403

Table 11 **Literature search: Cochrane Library**

Date	Search string	Results
15/05/2006	**#1** trandolapril (in all fields) AND verapamil (in all fields), (in all product	57
	#2 hypertension (in all fields, in all products)	20,917
	#3 #1 AND # 2	47
	Cochrane Reviews	2
	Other reviews	3
	Clinical trials	42

Table 12 Literature search: TGA Registration Dossier

Study types	Results
Pharmacodynamic	3
Pharmacokinetic	7
Clinical experience	25
Post-marketing experience	3

In total, 441 non-duplicate citations were identified by the literature search. Exclusion criteria were applied to the 441 identified citations in two stages: (i) to the title/abstracts; and (ii) to the full papers of those considered to be potentially relevant after the first pass (A record of the excluded studies is provided as an Appendix F to this submission). The exclusion criteria were as follows:

- Not a clinical study: excludes citations that do not report on the results of a clinical study conducted in humans.
- Wrong intervention: excludes studies in which verapamil/trandolapril is not used in combination.
- Wrong indications: excludes studies that are not conducted in subjects with hypertension.
- Wrong outcomes: excludes studies that do not report on hypertension outcomes.
- Not in English: excludes studies that are not published in English.
- Other: excludes studies for other reasons including duplicate data and no clinical data reported.
- In addition, after all trials which included a verapamil/trandolapril regimen were identified, studies which use any dosing strategy other than a fixed verapamil 240 mg/trandolapril 4 mg dose combination were excluded.

After the exclusion criteria were applied, three citations remained. The flow of exclusions are summarised in **Table13**.

Table 13 Exclusion of citations

Reason for exclusion	Title/abstract	Full paper/report
	441	*73*
Not a clinical study	109	2
Wrong intervention	18	0
Wrong indication	3	4
Wrong outcomes	2	0
Not in English	10	0
Other	3	1
Wrong dose	–	63
TOTAL	*73*	*3*

Table14 lists the studies excluded for the reason of "wrong dose". The most common dosing regimen used in the verapamil studies was verapamil 180 mg/trandolapril 2 mg. Some excluded studies examined the use of a regimen containing verapamil 240 mg and trandolapril 4 mg; however, this was within a flexible dosing framework with subjects titrated to dose based on response. It was not possible to identify which patients had received the verapamil 240 mg/trandolapril 4 mg combination from the studies. As TARKA® uses a fixed dose combination, and many of the subjects in these studies would not have received this exact combination, these studies were not considered relevant and have been excluded.

Table 14 Dosing regimens of studies excluded due to "wrong dose"

Study ID	Study report	Publications	Intervention	Control
Randomised controlled trials				
BENEDICT		Ruggenenti et al (2004)	Verapamil SR 180 mg/trandopril 2 mg	Trandopril 2mg, verapamil 240 mg, placebo
PRADID		Ruilope et al (2004)	Verapamil 180-240 mg/trandolapril 2 mg	Trandolapril 2 mg, placebo
-	-	Holzgreve et al (2003)	Dose level 1: verapamil 180 mg/trandolapril 1 mg; dose level 2 (non-responders): verapamil 180 mg/trandolapril 2 mg	Dose level 1: atenolol 50 mg/chlorthalidone 12.5 mg; dose level 2 (non responders): atenolol 100 mg/chlorthalidone 25 mg
INVEST	Abbott Scientific Report R&D/03/534 and Addendum	Pepine et al (2003); Elliott et al (2005); Bakris et al (2004)	CCB strategy (verapamil 240 mg ± trandolapril 2 mg ± HCTZ)	
-	-	Quiñones et al (2002)	Verapamil 180 mg/trandolapril 2 mg	Nifedipine 20 mg/atenolol 50 mg
PROCOPA	-	Ruilope et al (2002)	Verapamil 180 mg/trandolapril 2 mg (doubled at 4 weeks and halved at 8 weeks if poor tolerance)	Verapamil 240 mg/day, trandolapril 2 mg/day, atenolol 50 mg/day (doubled at 4 weeks and halved at 8 weeks if poor tolerance)
TRAVEND		Fernandez et al (2001)	Verapamil SR 180 mg/trandolapril 2 mg	Enalapril 20 mg/hydrochlorothiazide 12.5 mg
-	-	Mitrovic et al (2001)	Verapamil SR 180 mg/trandolapril 2 mg	Trandolapril 2 mg

Study ID	Study report	Publications	Intervention	Control
-	-	Cifková et al (2000)	Verapamil 180 mg/trandolapril 2 mg (single capsule)	Captopril 50 mg/hydrochlorothiazide 25 mg
-	-	Karlberg et al (2000)	Verapamil 180 mg/trandolapril 2 mg (single capsule)	Trandolapril 2 mg, verapamil 180 mg
EDICTA		Ruilope et al (1999)	Verapamil 180 mg/trandolapril 2 mg (single dose)	Maintained on previous monotherapy (mostly ACEI or CCBs)
-		Topouchian et al (1999)	Verapamil 180 mg/trandolapril 2 mg	Trandolapril 2 mg, verapamil 240 mg
VT067	Report CD98004	-	Verapamil SR 180 mg/trandolapril 2 mg (VeraTran)	Trandolapril 2 mg
-		Bakris et al (1998)	Verapamil SR 180-240 mg/trandolapril 2-4 mg	Trandolapril 2-8 mg, verapamil SR 180-360 mg
-	Report MPF/H 9503.	Breithaupt-Grogler et al (1998)	Trandolapril 1 mg/verapamil SR 180 mg	Metoprolol 100 mg/HCTZ 12.5 mg
-	Report MPF/K 9301.	Scholze et al (1998)	Verapamil SR 120 mg/trandolapril 0.5 mg; verapamil SR 180 mg/trandolapril 0.5 mg; verapamil SR 240 mg/trandolapril 0.5 mg; verapamil SR 120 mg/trandolapril 2 mg; verapamil SR 180 mg/trandolapril 2 mg; verapamil SR 240 mg/trandolapril 2 mg; verapamil SR 120 mg/trandolapril 8 mg, verapamil SR 180 mg/trandolapril 8 mg; verapamil SR 240 mg/trandolapril 8 mg	Trandolapril 0.5 mg, 2 mg, 8 mg; verapamil SR 120 mg, 180 mg or 240 mg; placebo
-	Report MPF/H 9506.	de Leeuw et al (1997)	Verapamil SR 180 mg/trandolapril 2 mg (single capsule?)	Atenolol 100 mg/chlorthalidone 25 mg, lisinopril 20 mg/HCTZ 12.5 mg, placebo
TV-50-HTN	Report TVN-50-HTN.	DeQuattro et al (1997); Levine et al (1997)	Verapamil SR 120 mg/trandolapril 0.5 mg; verapamil SR 180 mg/trandolapril 0.5 mg; verapamil SR 240 mg/trandolapril 0.5 mg; verapamil SR 120 mg/trandolapril 2 mg; verapamil SR 180 mg/trandolapril 2 mg; verapamil SR 240 mg/trandolapril 2 mg; verapamil SR 120 mg/trandolapril 8 mg, verapamil SR 180 mg/trandolapril 8 mg; verapamil SR 240 mg/trandolapril 8 mg	Verapamil SR 120 mg, 180 mg or 240 mg; trandolapril 0.5 mg, 2 mg 8 mg; placebo
-	Report MPF/H 9509.	Mancia et al (1997)	VeraTran 180/1 mg	Verapamil SR 180 mg, trandolapril 1 mg, placebo
-		Punzi et al (1997)	Dose stage 1: trandolapril 2 mg; dose stage 2 (non-responders): trandolapril 4 mg; dose stage 3 (non-responders): trandolapril 4 mg/verapamil 180 mg; dose stage 4 (non-responders): HCTZ	
-	Report MPF/H 9507.	Viskoper et al (1997)	Verapamil SR 180 mg/trandolapril 2 mg (single capsule)	Trandolapril 2 mg, verapamil SR 180 mg
-		Viskoper et al (1997)	Verapamil SR 180 mg/trandolapril 2 mg (single capsule)	Trandolapril 2 mg, verapamil SR 180 mg
-	Report MPF/H 9508.	Predel et al (1996)	Trandolapril 1 mg/verapamil 180 mg	Trandolapril 2 mg, atenolol 50 mg/chlortalidone 12.5 mg, placebo
-		Nalbantgil et al (1996)	Trandolapril 1 mg/verapamil SR 120 mg (single capsule)	Trandolapril 2 mg, verapamil SR 240 mg
-	Report MPF/H 9505.	Schneider et al (1996)	Verapamil 180 mg trandolapril 1 mg, increased after 4 weeks to verapamil 180 mg/trandolapril 2 mg in non-responders (single capsule)	Atenolol 50 mg/chlortalidone 12.5 mg, increased after 4 weeks to atenolol 100 mg/chlortalidone 25 mg in non-responders
VeraTran 082	Report MPF/H 9802.	-	Verapamil SR 240 mg/trandolapril 2 mg, bilayer tablet	Verapamil SR 240 mg, trandolapril 2 mg, placebo
VT020	Report R&D/02/698	-	VeraTran (verapamil SR 240 mg/trandolapril 2 mg)	Verapamil SR 240 mg
-	Report MPF/H 9504.	-	VeraTran (180/1)	trandolapril 1 mg, verapamil 180 mg, placebo

Study ID	Study report	Publications	Intervention	Control
-	Report MPF/H 9510.	-	Verapamil 180 mg/trandolapril 2 mg	Trandolapril 2 mg
	Report MPF/K 9007	-	Trandolapril 0.5 mg/verapamil SR 120 mg, trandolapril 1 mg/verapamil SR 240 mg	Trandolapril 1 mg, verapamil SR 240 mg
Case series				
-		Rubio-Guerra (2005)	Verapamil 180 mg/trandolapril 2 mg	None
-	-	Derici et al (2003)	Verapamil SR 180 mg/trandolapril 2 mg	None
-	-	Macías-Núñez et al (2003)	Verapamil 180 mg added to existing trandolapril treatment (dose not given) if elevated SCr. Withdrawn after 4 weeks if no improvement in blood pressure, continue for 8 weeks if improvement, Excluded if no normalisation of BP. If responders, then given fixed combination trandolapril 2 mg/verapamil 180 mg	None
-		Rubio Guerra et al (2002)	Verapamil 180 mg/trandolapril 2 mg (same capsule)	None
-		Adalet et al (2001)	Verapamil SR 180 mg/trandolapril 2 mg (single tablet)	None
-	-	Aksöyek et al (2001)	Verapamil SR 180 mg/trandolapril 2 mg	None
-	Report MPF/K 9310	Holzgreve et al (1999)	Titrated to individual dose: dose step 1 - verapamil SR 120 mg/trandolapril 0.5 mg; dose step 2 - verapamil SR 180 mg/trandolapril 1 mg; dose step 3 - verapamil SR 180 mg/trandolapril 2 mg (single capsules)	None
-		Aepfelbacher et al (1997)	Verapamil SR 180 mg/trandolapril 2mg once daily. If non-response then verapamil SR 240 mg/trandolapril 4 mg once daily. If non-response then verapamil SR 180 mg/trandolapril 2 mg/ twice daily	None
-	-	Skoularigis et al (1997)	Dose level 1: verapamil 180 mg/trandolapril 2 mg; dose level 2: verapamil 240 mg/trandolapril 4 mg; dose level 3: verapamil 360 mg/trandolapril 4 mg; dose level 4: addition of 12.5 mg HCTZ (single dose)	None
-	Report MPF/H 9401.	Oren et al (1996)	Verapamil 180 mg/trandolapril 1-2 mg	None
-	Report MPF/H 9501.	-	Dose level 1: verapamil SR 180 mg/trandolapril 0.5 mg; dose level 2: verapamil SR 180 mg/trandolapril 1.0 mg; dose level 3: verapamil SR 180 mg/trandolapril 2 mg (single capsule)	None
-	Report MPF/H 9502.	-	Titrated to individual dose: dose step 1 - verapamil SR 120 mg/trandolapril 0.5 mg; dose step 2 - verapamil SR 180 mg/trandolapril 1 mg; dose step 3 - verapamil SR 180 mg/trandolapril 2 mg (single capsule)	None
-	Report MPF/K 9303.	-	Trandolapril 1 mg/verapamil SR 180 mg	None
TV-31-HTN	1993	-	Dose level 1: trandolapril 0.5 mg/verapamil SR 120 mg; dose level 2: trandolapril 1 mg/verapamil SR 120 mg; trandolapril 2 mg/verapamil SR 120 mg; trandolapril 1 mg/verapamil SR 180 mg	None

2.2 Listing of all potentially relevant studies

Three studies (four citations) were identified which were considered potentially relevant to this submission: TV-51-HTN and The Study of Trandolapril/ verapamil-SR and Insulin Resistance (STAR). In addition, Study TV-4-CP was identified as providing potentially relevant data regarding the bioequivalence of the formulation used in TARKA® and trandolapril and verapamil-SR as monotherapies. The three studies are listed in **Table15**.

Table 15 Potentially relevant studies

Protocol number	Citation
TV-4-CP	Steady State determination of the Bioequivalence of a fixed tablet formulation of trandolapril and slow release verapamil (Isoptin-SR) vs. the combination of a trandolapril capsule with a verapamil tablet in healthy male subjects (Feb. 1995). Provided in Appendix D of the submission.
TV51	Double-blind, randomized, placebo-controlled, study to evaluate the safety and efficacy of oral trandolapril in combination with verapamil (Isoptin SR) (1993) provided in Appendix C of the submission. Messerli et al (1998) Effects of verapamil and trandolapril in the treatment of hypertension. American Journal of Hypertension 11: 322-327.
STAR	Bakris et al (2006) Differences in glucose tolerance between antihypertensive combination drugs in metabolic syndrome patients: results of STAR Meeting of the American Society of Hypertension, 2006. Abstract number: **[MP-50] A slide set is provided in Appendix E of the submission.**

2.3 Selection of the comparative randomised trials

TV-51-HTN is used as pivotal evidence of the comparative efficacy of the combination and monotherapies (see Appendix C). The Study of Trandolapril/ verapamil-SR and Insulin Resistance (STAR) will be used as supportive evidence (see Appendix E). The bioequivalence study (TV-4-CP) is not presented in detail but is provided as a reference in this submission to support the bioequivalence between the individual components of trandolapril 4mg and verapamil-SR 240mg given concomitantly are bioequivalent to TARKA® 4/240 (see Appendix D).

2.4 Assessment of the Measures Taken by Investigators to Minimise Bias in the Comparative Randomised Trials

Table16 presents a summary of the measures taken to minimise bias in the pivotal and supportive trial.

2.4.1 Randomisation

TV-51-HTN was randomised by secure, centralised, computer generated methods with randomisation lists for each study centre provided by Knoll pharmaceuticals. STAR was

randomised by secure, centralised, computer generated methods and randomisation was also provided to each study centre.

2.4.2 Adequacy of Follow-up

TV-51-HTN enrolled 631 patients after a placebo controlled run in period. A total of 50 patients(7.9%) withdrew from the study prior to completion. The most common reasons were adverse events, unsatisfactory response and protocol violations (see **Table 16** for details). All patients were evaluable and analysed using an ITT analysis.

STAR enrolled 240 patients after a washout period. A total of 54 (23%) patients withdrew from the study prior to completion. The most common reasons were adverse events, unsatisfactory response and protocol violations (see **Table 16** for details). The analysis was conducted using an ITT analysis. It should be noted that 6 patients dropped out due to cyclone Katrina in the US.

2.4.3 Blinding of Outcomes Assessment

TV-51-HTN was reported as a double blind study in which both the patient and observer were kept blind to the treatments given and as such was not subject to observer bias. The study did include a single blind (patient) run-period. STAR was a randomised, open-label study with blinded outcome evaluation. The study included an unblinded washout period of 4 weeks.

Table 16: Measures Taken by Investigators to Minimise Bias

Trial	Design*	Treatment†	N	Randomisation Details	N (%) Completed	N (%) Drop-outs	Reasons for Withdrawal N	Pop Asses (n)	Outcome Assessment
Key Trial									
TV-51-HTN	MC, R, DB, PG	1. Trandolapril 4mg/ day. 2. Verapamil SR 240mg/ day 3. Trandolapril 4mg/ day and 240mg/ day verapamil SR 4. Placebo Verapamil supplied as Isoptin SR the same form as in TARKA®	631	Computer generated randomisation by centre	581 (91.9)	50 (8.1%)	Adverse events-20 Unsatisfactory response- 12 Intercurrent medical problem-2 Failure to follow appointment schedule- 7 Therapy refusal-1 Administrative problems-2 Other- 6	ITT (631)	▪ Primary outcome was average sitting diastolic blood pressure in trough after 6 weeks of treatment (Week 10) ▪ Satisfactory therapeutic response was a reduction from baseline in average sitting diastolic blood pressure to lower than 90mmHg or a ≥10 mmHg decrease from baseline (Week 4) at endpoint.
Supplementary trial									
STAR	R, MC, open label, blinded outcome evaluation.	1. T/V 2/180 mg QD 2. L/H 50/12.5 mg QD	240	Computer generated randomisation by centre	186 (78%) 91 patients assigned to T/V and 95 patients assigned to L/H completed the study.	54 (22%)	Adverse events-21 Protocol, violation-2 Withdrew consent- 11 Lost to follow-up-11 Other- 6 Unknow-7	ITT	Primary: Percent change from Baseline to Week 52 or last measurement (Study End) using the 2-hour plasma glucose value post glucose load Secondary Efficacy Variables: •Achievement of JNC 7 BP goals, change in BP •Change in pulse rate •Fasting and postprandial concentrations during OGTT •Glucose AUC 0-120 •Insulin AUC 0-120 •Change in HbA1c

DB=Double Blind; R=Randomised; PG=parallel group; MC= Multicentre.

2.5 Characteristics of the Comparative Randomised Trials

Trial design and the characteristics of patients participating in the trials are presented in **Tables 17 and 18**.

2.5.1 Pivotal Trial design Characteristics

TV-51-HTN was a US, multicentre, randomised, double blind study with a parallel design. STAR was a prospective, randomised, open-label study with blinded outcome evaluation.

2.5.2 Pivotal Trials Patient Characteristics

TV-51-HTN was conducted in adult patients who had mild to moderate essential hypertension for 8 to 9 years with baseline mean diastolic blood pressure measures of greater than 95mmHg and less than 114 mmHg. The majority (87%) were white and a secondary cardiovascular diagnosis was reported in 55 patients (8.7%). The most prevalent secondary diagnoses were coronary artery disease (1.95) and valvular heart disease (1.4%).

STAR enrolled patients older than 21 years with the presence of the metabolic syndrome defined as:

- Fasting blood glucose ≥ 100 and ≤ 125 mg/dL;
- Documented controlled hypertension (SBP <140 mm Hg) requiring 2 meds with appropriate dose according the JNC 7, or uncontrolled BP on monotherapy (SBP ≥ 130 and <160 mm Hg),
- AND at least ONE of the following:
    - •HDL cholesterol <40 mg/dL in men, <50 mg/dL in women
    - •Total triglycerides ≥ 150 mg/dL
    - •Waist circumference >40 inches men, >35 inches women

2.5.3 Comparison of trial populations and proposed PBS population

In TV-51-HTN patients were mainly white with essential hypertension for 8- 9 years. They should be a population that reasonably reflects the PB population where listing is sought. Similarly STAR enrolled patients with metabolic syndrome and therefore should reflect an Australian population with he same characteristics.

2.5.4 Pivotal Trials Dosing Characteristics

TARKA® is available as a single trandolapril/verapamil-SR formulation in two strengths: 2/180mg tablets and 4/240mg tablets. This submission seeks listing for only the 4/240mg combination. TV-51-HTN provides a head to head comparison of the individual components (ie. 4mg trandolapril and 240mg verapamil-SR) versus the combination of 4/240mg trandolapril/verapamil-SR. The study did not use a combination tablet however the bioequivalence study provided in the references to this submission (TV-4-CP) demonstrated that the 4/240mg fixed tablets were found to be bioequivalent to the 4mg trandolapril and 240mg verapamil-SR for $AUC_{0\text{-}24h}$ and C_{max} for the active metabolites. It should also be noted that TV-51-HTN initiated patients on a combination of 4mg trandolapril and 120mg of verapamil-SR, this was titrated to 4mg/ 180mg verapamil-SR during the first week of the double blind period (week 5) and then a further titration to 4mg/ 240mg verapamil-SR occurred in the second week of the double blind period (week 6) of the study. The total duration of the double blind period was 6 weeks. The extent of exposure was 39.1 days for placebo, 38.2 days for 4mg trandolapril, 39.3 days for 240 verapamil-SR 240 and 27.4 days for the 4/ 240 combination.

In the open label STAR study, therapy was initiated using either the 2 mg trandolapril/ 180mg verapamil combination (TARKA®) or the 50mg losartan/ 12.5 hydrochlorothiazide combination (HYZAAR). The study included scheduled up titration at weeks 4 and 8. At the end of the study 91/119 (76.5%) of patients in the T/V arm and 89/121 of patients (73.6%) in the L/H arm were up-titrated to 4/240mg T/V and 100/25mg L/H, respectively. Doses of all treatments are within the dose guides of the current TGA listing for each product.

Table 17: Trial Characteristics of Key Trials

Trial	Study Design*	Treatment	Duration	Location of Trial	Inclusion Criteria
Key Trial					
TV-51-HTN	R, DB, MC, PGx4	1. Trandolapril 4mg/ day. 2. Verapamil SR 240mg/ day 3. Trandolapril 4mg/ day and 240mg/ day verapamil SR 4. Placebo	10 weeks (4 week placebo run-in followed by a 6 week double blind period).	**38 US centres**	▪ Successfully completed placebo run-in ▪ > 21 years of age and less than 50% above their ideal weight for their height (New York Met. Life Insurance Tables). ▪ Treated or newly diagnosed as having mild to moderate, no-labile, essential hypertension – mean supine and sitting diastolic BP in the range of 95-114mmHg.
Supplementary Trials					
STAR	R, MC, OL, blinded outcome evaluation, PGX 2	1. T/V 2/180 mg QD 2. L/H 50/12.5 mg QD	52 weeks (mean period of follow-up was 45.5 weeks in T/V group and 48.3 weeks in L/H group)	Not specified	•Presence of metabolic syndrome: –Fasting blood glucose ≥ 100 and ≤ 125 mg/dL –Documented controlled HTN (SBP <140 mm Hg) requiring 2 meds with appropriate dose according the JNC 7, or uncontrolled BP on monotherapy (SBP ≥ 130 and <160 mm Hg), AND at least ONE of the following: •HDL cholesterol <40 mg/dL in men, <50 mg/dL in women •Total triglycerides ≥ 150 mg/dL •Waist circumference >40 inches men, >35 inches women - SBP <180 mm Hg at randomization

DB=Double Blind; R=Randomised; PG=parallel group; MC= Multicentre; OL-open-label

Table 18: Patient Characteristics of trials

Trial	Treatment (N)	Age	Gender % males	Weight	Duration of hypertension (mean years)	Baseline sitting diastolic BP in mmHg (Trough Mean±SD)	Baseline sitting systolic BP in mmHg (Trough Mean±SD)
Key Trial							
TV-51-HTN	Trandolapril 4mg/ day.(159)	54.3 ± 11.0	67%	188.9lbs± 33.7	8.7	101.3± 5.0	151.8± 14.8
	Verapamil SR 240mg/ day (157)	53.8 ± 11.7	61%	191.0lbs ± 39.8	9.1	100.8± 4.7	151.1± 14.6
	Trandolapril 4mg/ day and 240mg/ day verapamil SR (163)	56.1 ± 11.6	59%	193.3lbs ± 38.1	9.6	101.4± 5.3	152.3± 14.5
	Placebo (152)	53.8 ± 11.8	68%	192.8lbs ± 38.9	9.7	100.5± 4.5	153.6± 13.4
Supplementary Trials							
STAR	1. T/V 2/180 mg QD	57.7 ± 10.3	46%	95.7kgs ± 21.8	NA	NA	146 ± 13
	2. L/H 50/12.5 mg QD	55.4 ± 9.7	51%	95.7kgs ± 21.8			145 ± 12

NA-Not available

2.6 Analysis of the Comparative Randomised Trials

Key Trial

The primary efficacy variable in TV-51-HTN was between-treatment comparisons at endpoint in decrease in mean trough sitting diastolic blood pressure. Secondary endpoints included:

- Proportion of responders at endpoint (response equating to a trough sitting diastolic blood pressure of <90 mmHg and/or a ≥10mmHg decrease from baseline).
- Between-treatment comparisons at endpoint in decrease in mean peak sitting diastolic blood pressure.
- Between-treatment comparisons at endpoint in decrease in mean trough and peak sitting, supine and standing diastolic blood pressure.
- Between-treatment comparisons at endpoint in decrease in mean trough and peak sitting, supine and standing systolic blood pressure.

A summary of the outcome measures and analysis of TV-51-HTN is provided in **Table 19.**

Supplementary Trial

The primary efficacy outcome in the STAR trial was percent change from Baseline to Week 52 or last measurement (Study End) using the 2-hour plasma glucose value post glucose load.

Secondary efficacy variables included the following:

- •Achievement of JNC 7 BP goals, change in BP
- •Change in pulse rate
- •Fasting and postprandial concentrations during OGTT
- •Glucose AUC 0-120
- •Insulin AUC 0-120
- •Change in HbA1c
- •Differences in lipid profile

Table 19 provides additional information on the outcome measures and analysis of STAR.

Table 19: Outcome Measures and Analysis of Key Trials

Trial	Primary Outcome Measure	Secondary Outcome Measure	Analysis Methods	Significance level	Population Assessed
Key Trials					
TV-51-HTN	Average sitting diastolic blood pressure in trough after 6 weeks of treatment (Week 10)	• Satisfactory therapeutic response was a reduction from baseline in average sitting diastolic blood pressure to lower than 90mmHg or a ≥10 mmHg decrease from baseline (Week 4) at endpoint. • Mean peak sitting diastolic blood pressure after 6 weeks of treatment (Week 10). • Trough to peak ratios-sitting diastolic blood pressure. • Mean change in sitting diastolic blood pressure at each visit (Peak and trough). • Mean change in diastolic blood pressure-trough and peak • Sitting, supine and standing systolic blood pressure between treatment comparisons at endpoint peak and trough. • Mean change in systolic blood pressure-trough and peak. • pulse rate.	Descriptive statistics Continuos variables were to be analysed by a one-way ANOVA and categorical variables by a chi-square test. Comparisons were to be made of the combination to each component monotherapy and of all active treatments to placebo. The above pair wise comparisons were to be carried out by comparing the least square means using Snappon's T5 test. The proportion of patients achieving a satisfactory therapeutic response to treatment was compared using the chi-square test for proportions.	Pair wise comparisons were to be carried out at the 0.05 level using a per comparison error rate. The comparisons were one sided because the guidelines are one sided in their definition. The study was powered to detect a difference of about 3.5mmHg with 80% power.	ITT (all patients with at least one post baseline visit were included in the efficacy analysis.

Trial	Primary Outcome Measure	Secondary Outcome Measure	Analysis Methods	Significance level	Population Assessed
Supplementary Trial					
STAR	• The primary efficacy outcome in the STAR trial was percent change from Baseline to Week 52 or last measurement (Study End) using the 2-hour plasma glucose value post glucose load.	Secondary Efficacy Variables included the following: • •Achievement of JNC 7 BP goals, change in BP • •Change in pulse rate • •Fasting and postprandial concentrations during OGTT • •Glucose AUC 0-120 • •Insulin AUC 0-120 • •Change in HbA1c • •Differences in lipid profile • •Biomarker variables (eg, hs-CRP) • •Differences in 24- hour ABPM	•Primary endpoint: Analysis of covariance with terms for baseline, treatment group, and centre. Similar models used for secondary endpoints. •Adverse events: Incidence between treatment groups compared using Fisher's Exact Test.	All tests two-tailed with alpha = 0.05 100 patients per treatment group provides 80% power to detect treatment difference of 10 mg/dL (6%) in 2-Hour OGTT mean change in blood glucose from Baseline to Study End	Intention to treat analysis: All patients who received at least one dose of study drug and for whom Baseline and study endpoint efficacy assessments were available Safety analysis: All patients who received at least one dose of study drug

2.7 Results of the Comparative Randomised Trials

2.7.1 Efficacy

Pivotal trial

Study TV-51-HTN measured efficacy as the change in blood pressure from baseline to end point and the rate of response. Response was defined as a diastolic blood pressure of less than 90mmHg and/ or a decrease in blood pressure of ≥10mmHg.

Diastolic Blood Pressure: Between treatment comparisons at endpoint- Trough

The results for sitting, supine and standing diastolic BP are summarised in **Figure 4**.

For the primary endpoint of sitting diastolic BP all active treatments groups had statistically significant ($p<0.01$) lower endpoint mean trough sitting diastolic BP compared to placebo (see **Fig.4**). At endpoint, the combination therapy had statistically significant ($p<0.01$) lower mean trough sitting diastolic BP compared to its monotherapies. The combination provided a further -3.6 mmHg reduction in BP versus trandolapril and a further -3.8 mmHg reduction compared to verapamil-SR.

The between-treatment comparisons for supine and standing at endpoint were similar to sitting BP with all treatment groups having statistically significant ($p<0.01$) lower mean trough supine and standing diastolic BP compared to placebo (see **Fig.4**). The combination therapy had statistically significant ($p<0.01$) lower mean trough supine and standing diastolic BP at endpoint compared to its monotherapies. The combination provided a further -4.2 (supine) and -3.6 mmHg (standing) reduction in BP versus trandolapril and a further -3.6 (supine) and -3.7 mmHg (standing) reduction compared to verapamil-SR.

Diastolic Blood Pressure: between treatment comparisons at endpoint- Peak

The results for sitting, supine and standing diastolic BP are summarised in **Figure 5**.

For the primary endpoint of sitting diastolic BP all active treatments groups had statistically significant ($p<0.01$) lower endpoint mean peak sitting diastolic BP compared to placebo (see **Fig.5**). At endpoint, the combination therapy had statistically significant ($p<0.01$) lower mean peak sitting diastolic BP compared to its monotherapies.

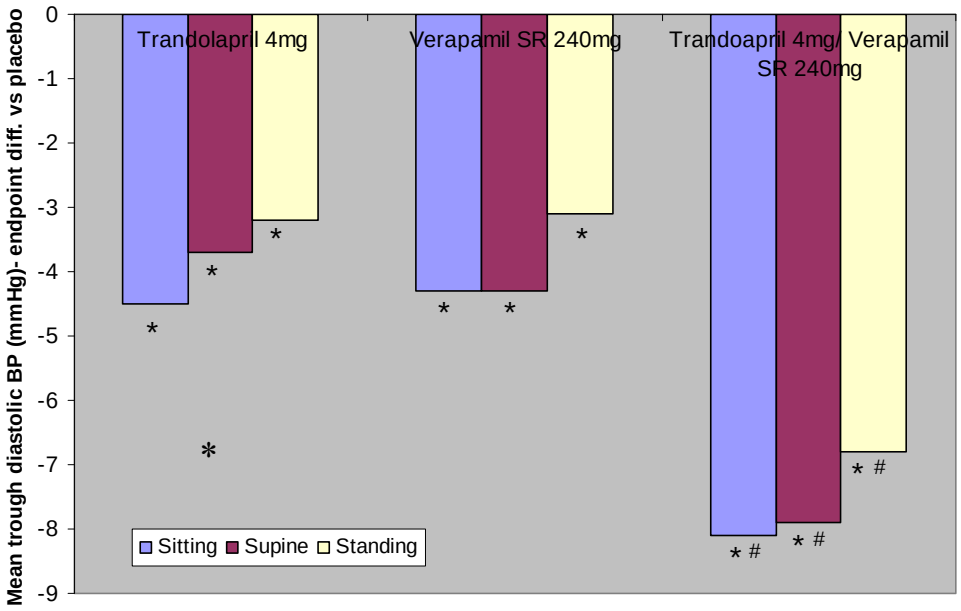


Figure 4: Mean sitting, supine and standing trough diastolic BP (mmHg)-Between treatment comparisons at endpoint vs. placebo. (*p<0.01 treatment versus placebo; # p<0.01 monotherapies versus combination)

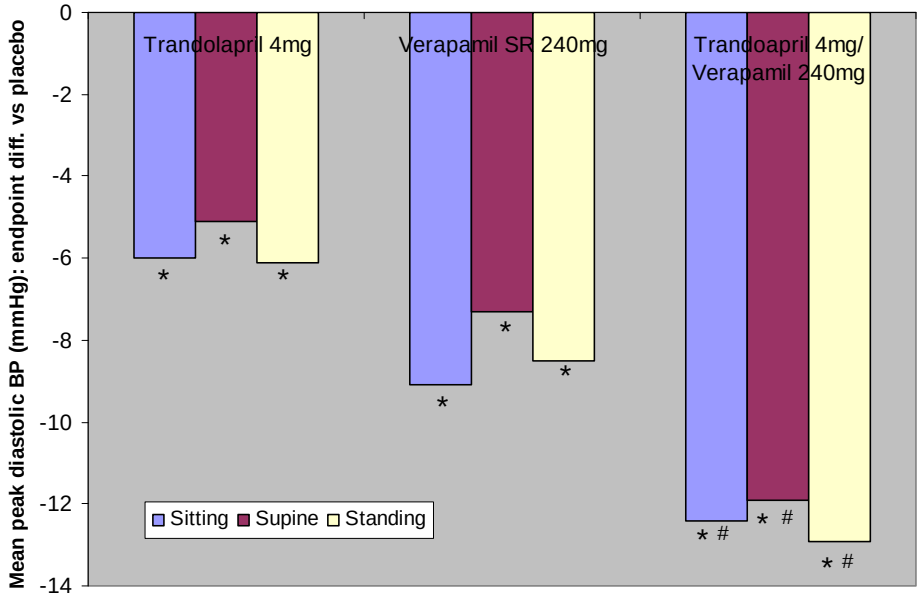


Figure 5: Mean sitting, supine and standing peak diastolic BP (mmHg)-Between treatment comparisons at endpoint vs. placebo. (*p<0.01 treatment versus placebo; # p<0.01 monotherapies versus combination)

The combination provided a further -4.6 mmHg reduction in BP versus trandolapril and a further -3.3 mmHg reduction compared to verapamil.

The between-treatment comparisons for supine and standing at endpoint were similar to sitting diastolic BP with all treatment groups having statistically significant ($p<0.01$) lower mean peak supine and standing diastolic BP compared to placebo (see **Fig.5**). The combination therapy had statistically significant ($p<0.01$) lower mean peak supine and standing diastolic BP at endpoint compared to its monotherapies. The combination provided a further -6.8 mmHg (supine and standing) reduction in BP versus trandolapril and a further -4.6 (supine) and -4.4 mmHg (standing) reduction compared to verapamil.

Systolic Blood Pressure: Between treatment comparisons at endpoint- Trough

The results for sitting, supine and standing systolic BP are summarised in **Figure 6**.

All treatment groups had statistically significant ($p<0.01$) lower endpoint mean trough sitting, supine and standing BP compared to placebo (see **Fig.6**). At endpoint the combination therapy had statistically significant ($p<0.01$ and $p<0.05$ for standing) lower mean trough systolic BP compared to its monotherapies. The combination provided a further -3.9 (sitting), -5.0 (supine) and -2.7 (standing) mmHg reduction in BP versus trandolapril and a further -4.9 (sitting), -7.5 (supine) and -5.6 (standing) mmHg reduction compared to verapamil.

Systolic Blood Pressure: between treatment comparisons at endpoint- Peak

The results for sitting, supine and standing systolic BP are summarised in **Figure 7**.

All treatment groups had statistically significant ($p<0.01$) lower endpoint mean peak sitting, supine and standing BP compared to placebo (see **Fig.7**). At endpoint the combination therapy had statistically significant ($p<0.01$) lower mean peak systolic BP compared to its monotherapies. The combination provided a further -8.8 (sitting), -8.0 (supine) and -8.0 (standing) mmHg reduction in BP versus trandolapril and a further –7.8 (sitting), -7.1 (supine) and -8.0 (standing) mmHg reduction compared to verapamil.

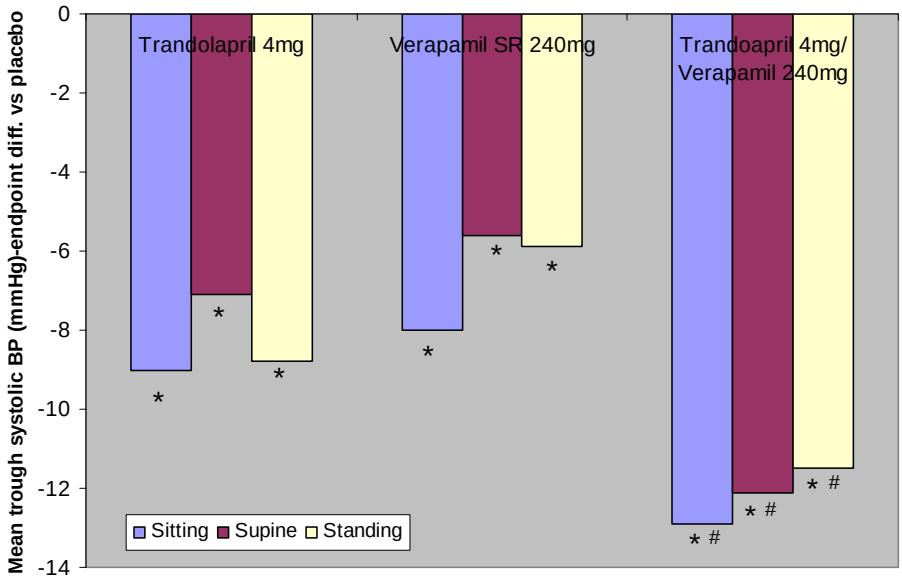


Figure 6: Mean sitting, supine and standing trough systolic BP (mmHg)-Between treatment comparisons at endpoint vs. placebo. (*p<0.01 treatment versus placebo; # p<0.01 monotherapies versus combination)

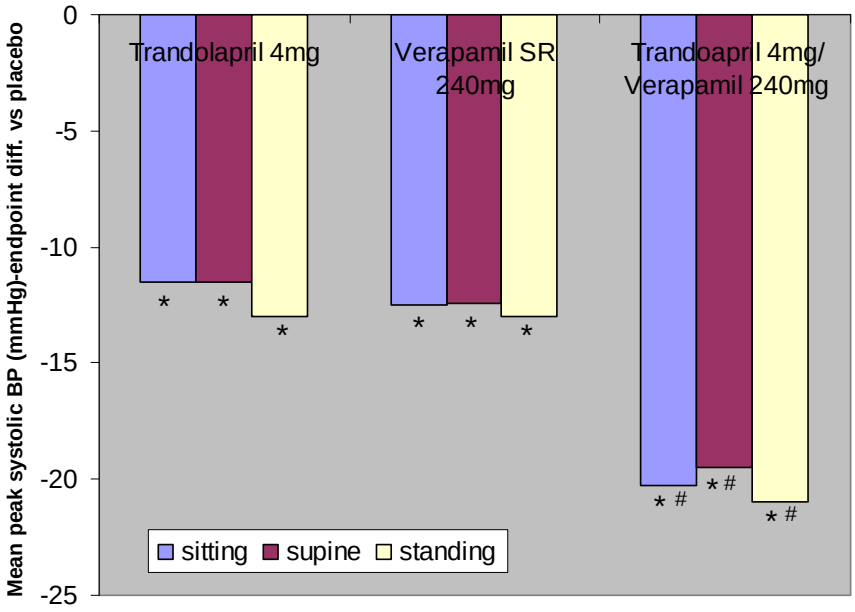


Figure 7: Mean sitting, supine and standing peak systolic BP (mmHg)-Between treatment comparisons at endpoint vs. placebo. (*p<0.01 treatment versus placebo; # p<0.01 monotherapies versus combination)

Responders at endpoint

Counts of responders at endpoint (patients with trough sitting diastolic BP < 90mmHg and/or a ≥ 10mm Hg decrease from baseline) at endpoint are presented in **Figure 8**. All active treatment groups had a statistically significant ($p<0.01$) greater proportion of responders compared to placebo. The combination therapy had a statistically significant ($p< 0.01$) greater proportion of responders (n=105/ 163, 64%) than either trandolapril (n=64/ 155, 41%) or verapamil-SR (n=57/155, 37%) monotherapy. When treated with the combination, an additional 23% (vs. trandolapril) and 27% (vs. verapamil) of patients were responders.

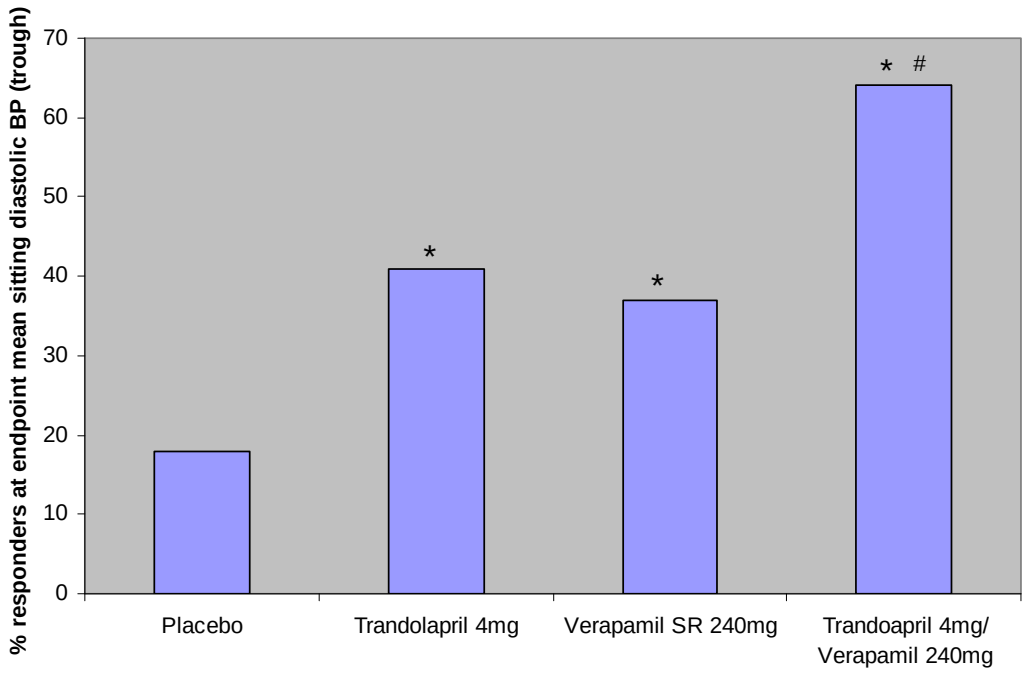


Figure 8: Percent responders at endpoint (patients with trough sitting diastolic BP < 90mmHg and/or a ≥ 10mm Hg decrease from baseline; *p<0.01 treatment versus placebo; # p<0.01 vs. either trandolapril or verapamil)

Other endpoints

The remaining endpoints all demonstrated similar results with significant improvements for the therapies over placebo and significant improvements for the combination over the individual therapies. This included all systolic and diastolic BP changes versus baseline measured each week during the study period. A complete set of efficacy endpoints is provided

in the trial report provided with this submission and **Table 22** provides a summary of all systolic and diastolic BP endpoints examined in TV-51-HTN.

Supplementary Trials

Although all patients in the STAR had hypertension, the focus of the study was not BP control but rather on glucose and insulin control in metabolic syndrome patients and there was no significant difference between TARKA® (verapamil-SR/trandolapril) and HYZAAR (losartan/HCTZ) treatment arms in systolic BP at either week 52 or at the end of the study. The primary endpoint in STAR was change from baseline to study end in 2-hour post-prandial plasma glucose level following an oral glucose tolerance test (OGTT). According to the 2006 clinical practice recommendation from the American diabetes Association OGTT is considered the gold standard for establishing a diagnosis of diabetes.

Primary endpoint: 2-Hour OGTT change in glucose from baseline

The results for the 2-hour OGTT adjusted mean change in blood glucose from baseline is presented in **Figure 9**. The mean blood glucose level for patients on TARKA® was 26 mg/dL compared to -3.8 mg/dL for patients on HYZAAR, this difference was highly significant ($p<0.001$). In addition, a significant difference between treatments was observed by week 12 of the 52 week study (see **Fig.9**).

Secondary endpoints

2-Hour OGTT change in insulin from baseline

The results for the 2-hour OGTT adjusted mean change in blood insulin from baseline is presented in **Figure 10**. The mean blood insulin level for patients on TARKA® was -5.0ulU/mL at study end compared to 14.0 ulU/mL for the HYZAAR combination. This difference was significant ($p<0.05$). In addition, a significant difference between treatments was observed by week 12 of the 52 week study (see **Fig.10**).

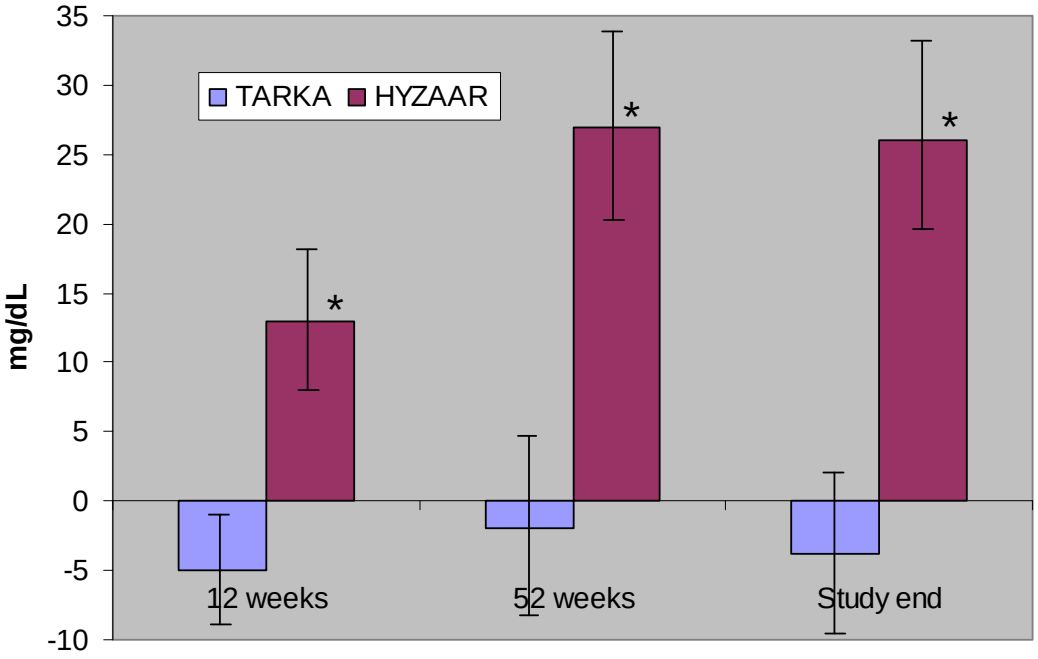


Figure 9: 2-hour OGTT adjusted# mean change in blood glucose from baseline. (# adjusted for baseline and centre; *p≤ 0.001 between treatment groups)

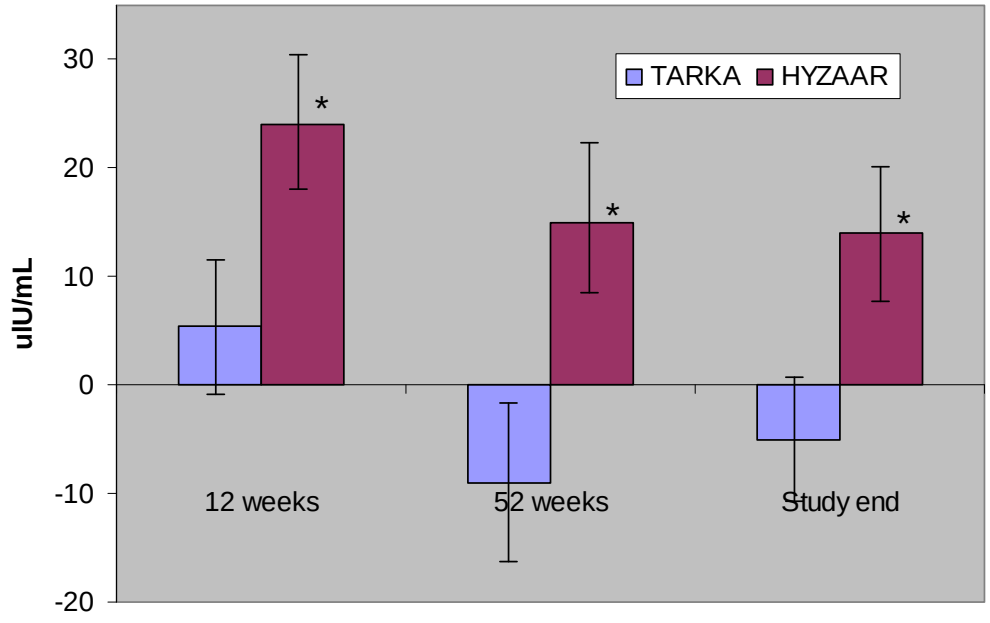


Figure 10: 2-hour OGTT adjusted# mean change in blood insulin from baseline. (# adjusted for baseline and centre; * p≤ 0.05 between treatment groups)

Percent change in HbA1c from baseline

The result for percent change from baseline in HbA1c is presented in **Figure 11**. At study end, a mean increase of 7.2 % was observed in patients on HYZAAR compared to only a 2.5% increase for patients on TARKA®. This difference was significant ($p<0.05$). A significant difference between treatments was observed by week 12 of the 52 week study (see **Fig.11**).

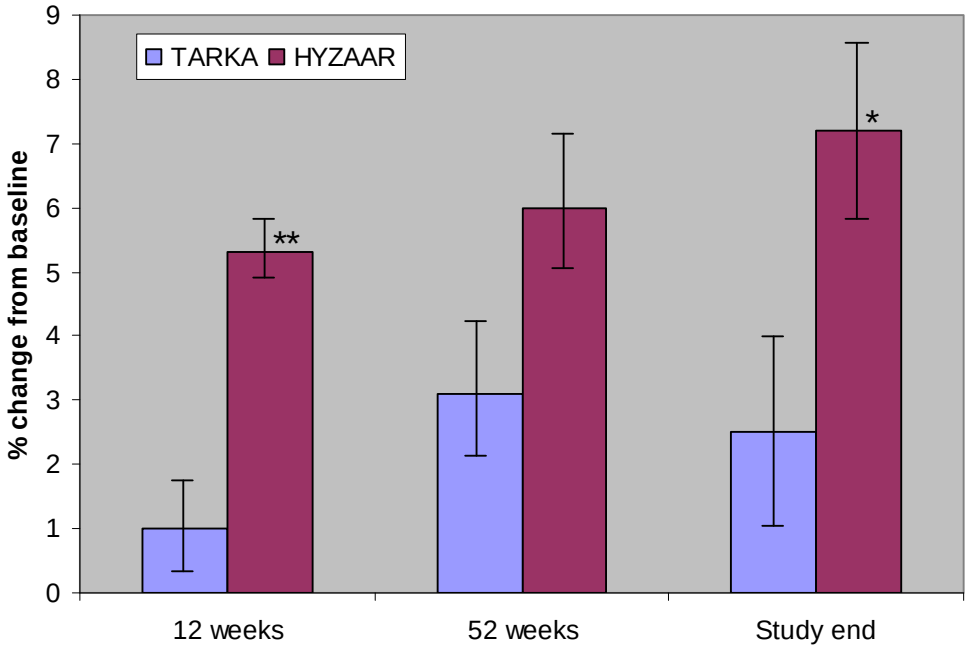


Figure 11: Adjusted# mean percent change in HbA1c from baseline. (# adjusted for baseline and centre; * p≤ 0.05 and ** p≤ 0.001 between treatment groups)

New onset diabetes (FBG ≥ 126 mg/dL)

The result for the percentage of patients with new onset diabetes is presented in **Figure 12**. At study end, 27% of patients on HYZAAR had new onset diabetes compared to 11.5% on TARKA®, an absolute reduction of 15.5% when TARKA® is compared to HYZAAR. This difference was significant ($p<0.01$). A similar significant difference between treatments was observed by week 12 of the 52 week study (see **Fig.12**).

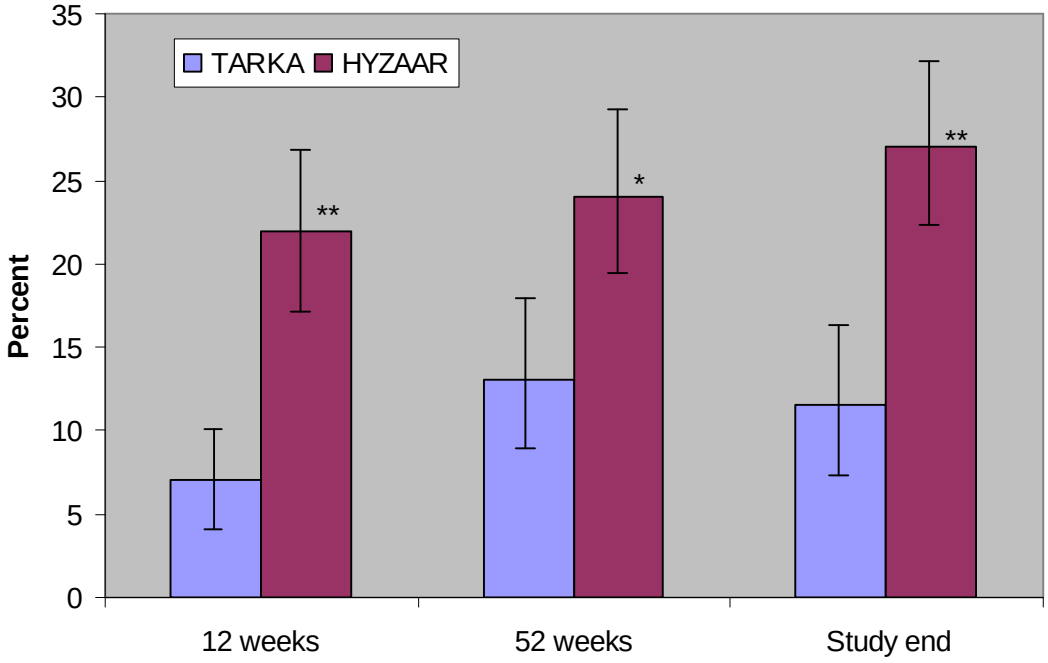


Figure 12: New onset of diabetes (FBG ≥ 126 mg/dL; * p≤0.05 and **p≤0.01 between treatment groups)

2.7.2 Safety Data

Pivotal study

In TV-51-HTN combination therapy was well tolerated with a low incidence of adverse events and no occurrence of unexpected adverse events. Seventy-two of 159 patients (45.3%) receiving trandolapril alone, 78 of 157 patients (49.7%) receiving verapamil-SR alone, 75 of 163 patients (46.0%) receiving any combination, and 67 of 152 patients (44.1%) receiving placebo experienced adverse reactions during the double blind phase of the TV-51-HTN. The incidence of adverse reactions reported in ≥ 3% of the patients during the double blind period are presented in the **Table 20**. The following significant differences were found in the study, cough (trandolapril (7.5%) vs. placebo (2.6%), p=0.05; combination (5.5%) vs. verapamil-SR (0.6%), p=0.012) and headache (combination (6.7%) vs. verapamil-SR (12.1%), p=0.021).

Table 20: Adverse events reported in ≥ 3% of patients in TV-51-HTN

Adverse Reaction	4mg Trandolapril N (%)	240 mg Verapamil SR N (%)	Any combination N (%)	Placebo N (%)
Headache	17 (10.7%)	19 (12.1%)	11 (6.7%)	18 (10.5%)
Upper respiratory tract infection	9 (5.7%)	14 (8.9%)	10 (6.1%)	12 (7.9%)
Cough	12 (7.5%)	1 (0.6%)	9 (5.5%)	4 (2.6%)
Dizziness	4 (2.5%)	6 (3.8%)	7 (4.3%)	4 (2.6%)
Fatigue	5 (3.1%)	2 (1.3%)	6 (3.7%)	4 (2.6%)
Chest pain	1 (0.6%)	4 (2.5%)	6 (3.7%)	1 (0.7%)
Joint pain	2 (1.3%)	0	6 (3.7%)	1 (0.7%)
Constipation	1 (0.6%)	6 (3.8%)	4 (2.5%)	2 (1.3%)
Diarrhoea	3 (3.1%)	1 (0.6%)	4(2.5%)	2 (1.3%)
Upper respiratory tract congestion	4 (2.5%)	1 (0.6%)	3 (1.8%)	5 (3.3%)
Nausea	5 (3.1%)	2 (1.3%)	2 (1.2%)	1 (0.7%)
Abdominal pain	5 (3.1%)	0	1 (0.8%)	2 (1.3%)
Oedema	2 (1.3%)	2 (1.3%)	1 (0.6%)	5 (3.3%)
Rash	5 (3.1%)	2 (1.3%)	0	2 (1.3%)

Discontinuations due to adverse reaction

Twenty one patients discontinued therapy because of adverse reactions, 4 patients receiving placebo, 7 receiving trandolapril, 7 receiving verapamil-SR and 3 receiving any combination. Most were considered probably not related to study medication. Five serious adverse events were reported with only two events; a patient with hypotension on 4 mg trandolapril and a patient with transient palpitations on combination therapy were considered "probably" related to active study drug. Detailed listings of all adverse events are provided in the study report provided as a reference in this submission.

Supplementary study

A summary of adverse events reported in ≥ 5% of patients in STAR are presented in **Table 21**. A significant difference was observed in cough and pain in the extremity. A total of 6 patients in each treatment arm had a serious adverse event.

Table 21: Adverse events reported in ≥ 5% of patients in STAR

Adverse Reaction	Trans/Ver N (%)	Los/ Hydro N (%)	P-value
Constipation	11 (9%)	4 (3%)	0.066
Cough	7 (6%)	1 (1%)	0.035
Diabetes mellitus	10 (8%)	16 (13%)	0.300
Dizziness	9 (8%)	5 (4%)	0.284
Dry mouth	8 (7%)	7 (6%)	0.796
Fatigue	6 (5%)	7 (6%)	1.000
Headache	6 (5%)	5 (4%)	0.768
Pain in extremity	6 (5%)	0	0.014
Sinusitis	6 (5%)	3 (2%)	0.331
Upper respiratory tract infection	7 (6%)	6 (5%)	0.783
Urinary tract infection	6 (5%)	6 (5%)	1.000

Orthostatic hypotension

Orthostatic reactions, defined as a decrease in standing systolic pressure of at least 20mmHg when changing from a supine to standing position was examined in TV-51-HTN. There was no significant difference between active treatments in the incidence of orthostatic symptoms or between the combination and the monotherapies.

Blood chemistry

The incidence of new glucose abnormalities was statically significant different among the treatment groups (Increased or decreased glucose: trandolapril 6 (3.9%), verapamil-SR 6 (3.6%), combination 11 (6.7%), placebo 17 (11.2%); p=0.023). No other significant differences were found.

2.8 Interpretation of the Results of the Comparative Randomised Trials

A summary of the comparative changes in diastolic and systolic BP from baseline to endpoint for TV-51-HTN are summarised in **Table 22**. As noted in the PBAC Public Summary Document (PSD), "a 2 mmHg margin is considered the minimum clinically acceptable difference in diastolic BP (DBP)". The results of the head-to-head study show that both 240 mg verapamil-SR and 4 mg trandolapril as monotherapy provide a statistically significant and clinically acceptable difference in blood pressure (sitting-trough) over placebo (4.3 and 4.5 mmHg reductions respectively). Furthermore, the magnitude of the difference in DBP between the combination of 240 mg verapamil-SR with 4 mg trandolapril and both components as monotherapy is also statistically and clinically acceptable difference (approximately 3.8 and 3.6 mmHg respectively). Similar results are seen when the systolic blood pressure (SBP) results are examined. In summary TV-51-HTN demonstrates a significant difference on all systolic and diastolic blood pressure (BP) endpoints when the combination is compared to the monotherapies and shows that there is clear "additive beneficial effectiveness of the components" in the combination product.

Based on the results of TV-51HTN the category that best describes TARKA® is:

(i) The combination is significantly more effective than the individual components given as monotherapy and is no worse for efficacy and safety than the individual components given concomitantly.

Table 22: Baseline-Endpoint Changes in Blood pressure for pivotal clinical study TV-51-HTN

Blood Pressure	Treatment	Comparison	Comparative difference in BP from baseline in mmHg					
			Diastolic			Systolic		
			Sitting	Supine	Standing	Sitting	Supine	St
Trough	Trandolapril 4mg	Placebo	**-4.5**	**-3.7**	**-3.2**	**-9.0**	**-7.1**	
	Verapamil SR 240mg	Placebo	**-4.3**	**-4.3**	**-3.1**	**-8.0**	**-5.6**	
	Trandoapril 4mg/ verapamil-SR 240	Placebo	**-8.1**	**-7.9**	**-6.8**	**-12.9**	**-12.1**	
	Trandoapril 4mg/ verapamil-SR 240	Trandoapril 4mg	**-3.6**	**-4.2**	**-3.6**	**-3.9**	**-5.0**	
	Trandoapril 4mg/ verapamil-SR 240	Verapamil -SR 240 mg	**-3.8**	**-3.6**	**-3.7**	**-4.9**	**-7.5**	
Peak	Trandolapril 4mg	Placebo	**-6.0**	**-5.1**	**-6.1**	**-11.5**	**-11.5**	
	Verapamil SR 240mg	Placebo	**-9.1**	**-7.3**	**-8.5**	**-12.5**	**-12.4**	
	Trandoapril 4mg/ verapamil-SR 240	Placebo	**-12.4**	**-11.9**	**-12.9**	**-20.3**	**-19.5**	
	Trandoapril 4mg/ verapamil-SR 240	Trandoapril 4mg	**-6.4**	**-6.8**	**-6.8**	**-8.8**	**-8.0**	
	Trandoapril 4mg/ verapamil-SR 240	Verapamil -SR 240 mg	**-3.3**	**-4.6**	**-4.4**	**-7.8**	**-7.1**	

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(112)

AstraZeneca

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LMS. J. nr.: 5315-9

Lægemiddelstyrelsen
Att. Elisabeth Thomsen
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09.12.2008

Partshøring – Revurdering af tilskudsstatus for kombinationslægemidler i ATC-gruppe C02, C03, C07, C08 og C09 Logimax - Supplerende indstilling fra Medicintilskudsnævnet

Ved brev af 24 november 2008 har Lægemiddelstyrelsen anmodet AstraZeneca A/S om eventuelle bemærkninger til den supplerende indstilling dateret 2. september 2008.

AstraZeneca skal medgive, at der en væsentlig prisforskel imellem behandling med Logimax og en tilsvarende behandling med de to indholdsstoffer givet som generiske lægemidler.

'Adherence' til en given behandling er afhængig af, hvor mange tabletter der skal indtages og forskellen imellem 1 og 2 forskellige tabletter dagligt er formentlig beskeden bortset fra hos ganske få problempatienter.

Logimax anvendtes i 2007 af 1200 patienter. Logimax har indikationen hypertension, hvilket ikke udelukker, at Logimax kunne være den fortrukne behandling til en undergruppe af hypertensionspatienter, der også lider af angina pectoris. Hvis dette er tilfældet, vil en ændring i behandling fra Logimax til en tilsvarende behandling baseret på to lægemidler indebære en risiko, idet indtagelse af felodipin uden samtidig indtagelse af metoprolol vil kunne udløse angina pectoris anfald.

Det bør således overvejes, om de 1200 patienter, der i dag behandles med Logimax, tilhører en undergruppe af hypertonikere, der har specielt behov for enten at modtage en compliance fremmende behandling eller har et specielt terapeutisk krav om at indtage metoprolol og felodipin samtidigt, jævnfør ovenfornævnte tilfælde med hypertension kompliceret med angina pectoris.

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AstraZeneca

AstraZeneca finder således, at der er særlige forhold i relation til Logimax – nemlig de ovenfor nævnte – som kan begrunde prisforskellen.

AstraZeneca ser frem til, at Lægemiddelstyrelsen tager ovenstående synspunkter i betragtning under den fortsatte evaluering af tilskudsstatus for ATC-gruppe C02, C03, C07, C08 og C09

Venlig hilsen,
AstraZeneca A/S

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PARANOVA

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CVRnr. 18139480

Ballerup, d. 3. december 2008

J.nr. 5315-9 – Partshøring – Revurdering af tilskudsstatus for kombinationslægemidler i ATC-gruppe C02, C03, C07, C08 og C09 - Logimax

Lægemiddelstyrelsen har i brev af 24. november 2008 opfordret Paranova Danmark A/S (herefter "Paranova") til at sende sine eventuelle bemærkninger til styrelsens overvejelser om revurdering af tilskudsstatus for lægemidler i ovennævnte ATC-grupper.

Paranova bidrager som parallelimportør af lægemidler til priskonkurrencen på markedet for receptpligtige, patenterede lægemidler, men Paranova deltager ikke i udvikling og produktion af lægemidler. Paranova har derfor ingen bemærkninger til Medicintilskudsnævnets og Lægemiddelstyrelsens lægefaglige vurdering af lægemidlerne og deres anvendelse.

Paranovas virksomhed drives i sagens natur med udgangspunkt i lægemidlernes kendte tilskudsstatus, og dette indebærer, at der i forbindelse med indkøb af lægemidlerne og tilpasning af disse til det danske marked i form af ompakning eller etikettering foretages opbygning af lagre.

Da en ændret tilskudsstatus for et lægemiddel har meget stor betydning for salget heraf, må det forventes, at styrelsens revurdering af tilskudsstatus for ovennævnte lægemidler vil medføre et betydeligt økonomisk tab for Paranova, medmindre den ændrede tilskudsstatus varsles i så tilpas god tid, at Paranova har mulighed for at indrette sin virksomhed herpå. I tilknytning hertil bemærkes, at den ændrede tilskudsstatus påvirker alle markedsdeltagere, og at markedet vil blive oversvømmet af lægemidler, hvis ændringen indføres med meget kort varsel.

Paranova skal derfor henstille, at styrelsen ikke reviderer lægemidlers tilskudsstatus med et varsel på under 6 måneder fra den endelige beslutning træffes.

Venlig hilsen
Paranova Group A/S

Kim Jensen
Advokat

Lægemiddelstyrelsen
Axel Heides Gade 1
2300 København S
Att. Elisabeth Thomsen

19 DEC. 2008

Frederiksberg, 8 December, 2008

Re: Coversical®

Reference is made to the Danish Medicines Agency's (DMA) letter of 24 November 2008 asking for our comments not later than 11 December 2008.

We refer to our letter of 3 October 2008.

Surprisingly the DMA has not in its letter taken our comments on class effect into consideration but merely refers to the Reimbursement Committee's referrals to the class effect within the group of ACE inhibitors in its recommendations of 29 January 2008 and 2 September 2008.

It is very clear from this that the Reimbursement Committee has not taken our previous comments on class effect (in the letter of 3 October 2008) into consideration. Neither has the DMA which merely makes reference to general comments. Apparently the DMA has not made an evaluation of Coversical and the class effect themselves despite the fact that class effect is also based on legal ground.

Coversical was granted general reimbursement on 19 September this year. In this connection the DMA has taken into consideration that the drug has a certain and valuable therapeutic effect on a well-defined indication, and that the price of the drug is proportionate to its therapeutic value. Servier is still without an explanation on which this evaluation has changed since 19 September and would like the DMA's comments on this.

In the Reimbursement Committee's meeting on 21 October 2008 it was discussed whether the DMA should have meetings with stakeholders before a decision of de-reimbursement was taken, cf. minutes of RC's meeting no 310. In the minutes it is mentioned that requests for meetings will be considered individually. Servier has previously asked for a meeting regarding Coversyl without getting any response but has been informed that no meetings will be held in connection with the re-evaluation of the reimbursement for drugs for cardiovascular diseases. Based on this Servier would like to repeat the request for a meeting concerning both concerning Coversyl and Coversical.

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Please do not hesitate to contact me if you have any questions concerning the above.

Best regards,
Servier Danmark A/S

Philip Van Muylders
General Manager