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Fixed Combination Verapamil SR/Trandolapril

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Contents

Abstract

▲ Verapamil sustained-release (SR)/trandolapril is a combination of a phenylalkylamine calcium antagonist and an angiotensin converting enzyme inhibitor for the management of essential hypertension.

▲ Verapamil SR/trandolapril does not adversely influence glucose, insulin or lipid parameters in patients with mild to moderate essential hypertension and type 2 (non-insulin-dependent) diabetes mellitus with or without elevated cholesterol and/or triglyceride levels.

▲ Verapamil SR/trandolapril reduces proteinuria to a greater extent than the individual components in patients with diabetic or non-diabetic proteinuria.

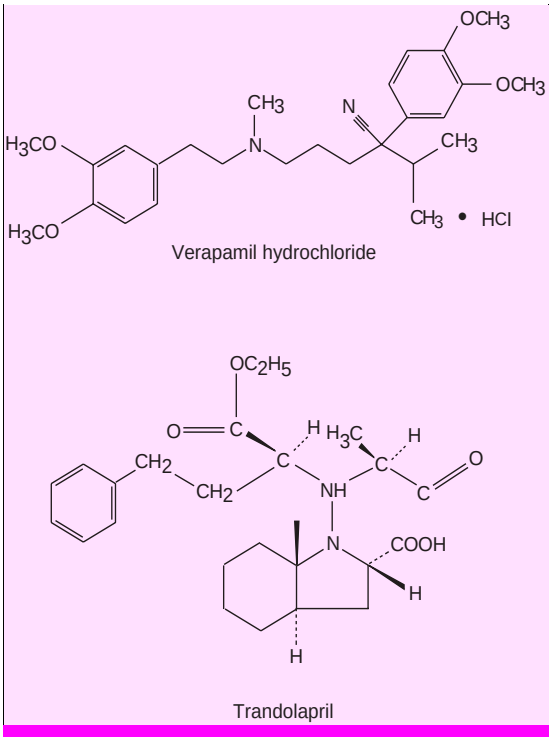
▲ The antihypertensive efficacy of once daily verapamil SR/trandolapril (180/1 or 180/2mg) for 8 weeks or 6 months is similar to that of atenolol/ chlorthalidone (100/25mg) and lisinopril/hydrochlorothiazide (20/12.5mg), and was at least as good as that of metoprolol/hydrochlorothiazide (100/12.5mg) in a small trial.

▲ The reduction in sitting or supine diastolic and systolic blood pressure is greater after verapamil SR/trandolapril (180/2 to 240/4mg) than after monotherapy with verapamil SR (180 and 240 mg/day) or trandolapril (2 to 8 mg/day).

▲ Fewer cardiac events occurred after verapamil SR/trandolapril (240/1 to 360/2 mg/day) than after trandolapril (1 to 2 mg/day) in postmyocardial infarction patients with congestive heart failure.

▲ The incidence of adverse events after verapamil SR/trandolapril is similar to that of comparator drugs and the individual components of the combination.

Features and properties of verapamil SR/trandolapril	
Indications	
Essential hypertension	Launched
Mechanism of action	
Combination of phenylalkylamine calcium antagonist and angiotensin converting enzyme inhibitor	Dilation of peripheral arterioles by inhibition of calcium ion influx (verapamil) and by inhibition of the renin-angiotensin-aldosterone system (trandolapril)
Dosage and administration	
Recommended dosage	180/2mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (combined values of the individual active components, verapamil and trandolaprilat, provided)	
Time to peak plasma concentration	4 to 6h (trandolaprilat) 4h (verapamil)
Plasma protein binding	>80% (trandolaprilat) 90% (verapamil)
Renal clearance	10 to 15% of a trandolaprilat dose and 3 to 4% of a verapamil dose is excreted unchanged in the urine
Elimination half-life	16 to 24h (trandolaprilat) 8h (verapamil)
Adverse events	
Most frequent	Constipation, cough, headache, dizziness, asthenia, nausea
Serious events	First degree AV-block



Verapamil/trandolapril

The fixed combination of sustained-release (SR) verapamil and trandolapril incorporates a phenylalkylamine calcium antagonist with an angiotensin converting enzyme inhibitor.

Combination therapy is particularly useful in patients with severe hypertension or target organ damage. Additionally, combination therapy may be necessary in many patients with hypertension in order to achieve optimum blood pressure control,[1] and it may be a reasonable treatment alternative to single-agent first-line therapy in the early management of hypertension if the theoretical expectation of increased response rates and reduction in adverse events is attained (reviewed by Neutel et al.[2] and Kaplan[3]). Furthermore, the use of a fixed combination may improve compliance.

In patients with congestive heart failure after myocardial infarction, the main aim of drug treatment is to prevent cardiac events, thus reducing morbidity and mortality (reviewed by Renkin,[4] Hansen[5] and Cleland[6]).

1. Pharmacodynamic Profile

Effects on Left Ventricular (LV) Function

- In a noncomparative trial, verapamil slow-release (SR)/trandolapril 180/2mg once or twice daily or 240/4mg once daily for 12 weeks significantly improved the echocardiographic features of LV function in 14 patients with mild to moderate essential hypertension. LV septal and posterior wall thicknesses were significantly reduced by about 8% ($p < 0.007$ and 0.009, respectively) and LV mass and mass index by about 9% ($p < 0.007$ and 0.004, respectively).[7]

- In another nonblind, noncomparative study, verapamil SR/trandolapril 180/2mg (once daily for 2 weeks increasing to twice daily for 10 weeks) increased exercise duration (6.9 to 7.7 minutes, $p < 0.01$) and the ratio of exercise to resting rate-pressure product (2.21 to 2.53, $p < 0.02$) in 14 patients with angina pectoris and a LV ejection fraction of <40%. In addition, LV ejection fraction and LV wall motion index significantly increased from 28.2 to 35.2% ($p < 0.03$) and 1 to 1.2 ($p < 0.03$), respectively.[8]

Effects on Heart Rate

- In general, verapamil SR/trandolapril 180/1 to 240/4mg once daily did not significantly alter heart rate in patients with mild to severe essential hypertension (see section 3 for study details).[9-13]

- In a comparative study with other once daily combination treatments, neither verapamil SR/trandolapril 180/1 or 180/2mg nor lisinopril/hydrochlorothiazide 20/12.5mg significantly affected heart rate but metoprolol/hydrochlorothiazide 100/12.5mg and atenolol/chlorthalidone 100/25mg significantly decreased it by about 9 to 10 beats/min.[9,10]

- In 1 large trial (n = 234), heart rate was significantly reduced by verapamil SR/trandolapril 180/1mg and verapamil 180mg once daily but not by trandolapril 1mg daily.[14]

Effects on Lipid and Glucose Metabolism

• Verapamil SR/trandolapril (mean dose 180/1.6 mg/day for 12 weeks[15] or 180/1 mg/day for 8 weeks[16]) did not adversely affect glucose, insulin or lipid parameters in 24[15] or 46[16] patients with mild to moderate hypertension and type 2 (non-insulin-dependent) diabetes mellitus. In 1 study, patients had elevated baseline total cholesterol (5.7 to 5.8 mmol/L) and/or triglyceride levels (2.3 to 2.8 mmol/L).[15] In these patients, atenolol/chlorthalidone, but not verapamil SR/trandolapril, significantly increased triglyceride levels and decreased high density lipoprotein levels ($p \leq 0.03$ *vs* baseline).[15]

• Trandolapril 1 mg/day, but not verapamil SR 180 mg/day or the verapamil SR/trandolapril combination, increased insulin sensitivity by 47% ($p = 0.0015$ *vs* baseline) in patients with hypertension and type 2 diabetes mellitus.[16] In contrast, atenolol/chlorthalidone (mean dose 71/18 mg/day) decreased insulin sensitivity by 62.5% ($p < 0.05$ *vs* baseline).[15] Changes in insulin sensitivity, fasting plasma glucose and area under the glucose concentration-time curve differed significantly between the atenolol/chlorthalidone and verapamil SR/trandolapril groups ($p < 0.05$).[15]

• In a small study in 63 patients with hypertension, insulin-stimulated glucose uptake increased after verapamil SR/trandolapril 180/1 or 180/2 mg/day (from 4.9 to 5.2 mg/min/kg/100mU) but decreased (from 4.9 to 4.5 mg/min/kg/100mU) after hydrochlorothiazide/amiloride 25/2.5 or 50/5 mg/day. Furthermore, fasting plasma glucose levels were higher in hydrochlorothiazide/amiloride than in verapamil SR/trandolapril recipients (5.7 *vs* 5.4%, $p < 0.001$).[17]

Effects on Renal Function

• Verapamil SR/trandolapril 180/2mg daily for 6 weeks significantly reduced proteinuria in 11 patients with non-diabetic proteinuria, most of whom were normotensive. This reduction was significantly greater than in verapamil 360 mg/day recipients and equivalent to that in patients receiving trandolapril 4 mg/day.[18]

• In another trial, the 62% reduction in proteinuria with verapamil SR/trandolapril (mean dose 219/2.9 mg/day for 1 year) was significantly greater than that reported after monotherapy with verapamil (mean dose about 315 mg/day) [27%] or trandolapril (mean dose 5.5 mg/day) [33%] in 37 hypertensive patients with nephropathy secondary to type 2 diabetes mellitus (both $p < 0.001$).[19]

• In patients with mild to moderate hypertension and type 2 diabetes mellitus, albuminuria significantly decreased (median change 33%, $p < 0.025$ *vs* baseline) in 10 of 12 verapamil SR/trandolapril recipients (mean dose 180/1.6 mg/day for 12 weeks) but in none of the 12 patients receiving atenolol/chlorthalidone (mean dose 71/18 mg/day). Four verapamil SR/trandolapril recipients and 8 patients receiving atenolol/chlorthalidone were initially hyperalbuminuric.[15]

2. Pharmacokinetic Profile

• After oral administration, 90% of verapamil SR is absorbed. Verapamil undergoes extensive first-pass metabolism and has a low absolute bioavailability of 22% (range 10 to 35%) which may increase to 30% after long term administration.[20]

• Trandolapril is a prodrug and is hydrolysed to the active metabolite trandolaprilat; 40 to 60% of active drug is absorbed after oral administration. The plasma half-life of trandolapril is 1 hour. The maximum plasma concentration (C_{max}) is achieved 4 hours after verapamil, 30 minutes after trandolapril and 4 to 6 hours after trandolaprilat. The absorption of neither drug is affected by the presence of food.[20]

• 90% of verapamil and more than 80% of trandolaprilat is bound to plasma proteins. Steady state is achieved after 3 to 4 days with verapamil and 4 days with trandolaprilat.[20]

• Only 3 to 4% of a verapamil dose is excreted unchanged in the urine: norverapamil, one of the 12 metabolites found in the urine, has 10 to 20% the activity of verapamil. The renal clearance of

trandolaprilat is linearly related to creatinine clearance (CL_{CR}). 10 to 15% of the trandolaprilat dose is excreted unchanged in the urine. The elimination half-life ($t_{½}$) is 16 to 24 hours for trandolaprilat and about 8 hours for verapamil.[20]

- Verapamil kinetics are unaffected by renal impairment but the bioavailability and $t_{½}$ may increase in liver cirrhosis. In patients with CL_{CR} ≤30 ml/min the plasma concentration of trandolaprilat increases. However, after long term administration in these patients, the time to reach steady state is unaltered relative to patients with normal renal function (4 days). The plasma concentrations of trandolapril and trandolaprilat and the renal excretion of trandolaprilat increase in patients with cirrhosis. The kinetics of all 3 agents are unaltered in patients with compensated hepatic dysfunction.[20]

- In 10 patients with fatty liver disease, the pharmacokinetics of verapamil were not significantly altered but the C_{max} and area under the concentration-time curve (AUC) of trandolaprilat increased by 42 and 30%, respectively, after verapamil SR/trandolapril 180/1 mg/day. However, no significant changes were observed in blood pressure, heart rate or the PQ interval.[21]

3. Therapeutic Trials

Essential Hypertension

Dose-Ranging Studies

- In two 6-week, double-blind, randomised, placebo-controlled, dose-ranging studies, the optimal combinations of verapamil SR/trandolapril were determined to be 180/1 (this dose is not marketed), 180/2, 240/2 and 240/8 mg/day in 424[22] and 723[23] patients with mild to moderate essential hypertension.

Comparison with Other Combination Treatments

- In a randomised, double-blind study, verapamil SR/trandolapril 180/2mg once daily for 8 weeks reduced sitting diastolic (DBP) and systolic (SBP) blood pressures to a similar extent to atenolol/chlorthalidone 100/25mg once daily and lisinopril/hydrochlorothiazide 20/12.5mg once daily and to a greater extent than placebo in 205 patients with mild to moderate essential hypertension (fig. 1a). Mean baseline sitting DBP ranged from 106 to 107mm Hg and SBP from 169 to 171mm Hg in the treatment groups.[9]

- In contrast, in a small, randomised, double-blind study with no placebo control, verapamil SR/trandolapril 180/1mg once daily for 6 months decreased sitting DBP (from about 101 to 87mm Hg, $p < 0.02$ *vs* metoprolol/hydrochlorothiazide) but not SBP to a significantly greater extent than metoprolol/hydrochlorothiazide 100/12.5mg once daily (from about 101 to 92mm Hg) in 40 patients with mild to moderate essential hypertension.[10]

- The percentage of verapamil SR/trandolapril recipients with normalisation of blood pressure (defined as a DBP <90mm Hg) or showing a response to treatment (defined as a decrease in DBP by ≥10mm Hg and/or normalisation of blood pressure) was similar to that observed after atenolol/chlorthalidone, lisinopril/hydrochlorothiazide and metoprolol/hydrochlorothiazide, and significantly greater than after placebo (fig. 1b and c).[9]

Comparisons with Verapamil or Trandolapril Monotherapy

- The treatment phase of studies presented in this section was generally preceded by a 3- to 28-day placebo run-in period. All but 1 study[24] in patients with mild to moderate essential hypertension were double-blind and randomised.[11,13,14] One trial examined the efficacy of verapamil SR/trandolapril in Black patients only.[24]

- Mean baseline sitting DBP ranged from 100 to 104mm Hg[11,14] and SBP from about 151 to 165mm Hg[11,13,14] In 1 trial,[13] some patients, who were included in a separate report,[25] had a baseline sitting DBP of <100mm Hg.

- In a nonblind, nonrandomised study in 87 patients (30 of whom were Black) with severe essential hypertension (mean baseline SBP and DBP were about 182 and 120mm Hg, respectively), verapamil SR/trandolapril 180/4mg or 180/8mg once daily reduced supine DBP and SBP (by about 14 and 15mm Hg, $p < 0.001$ *vs* monotherapy) to a significantly greater extent than trandolapril 2, 4 or 8

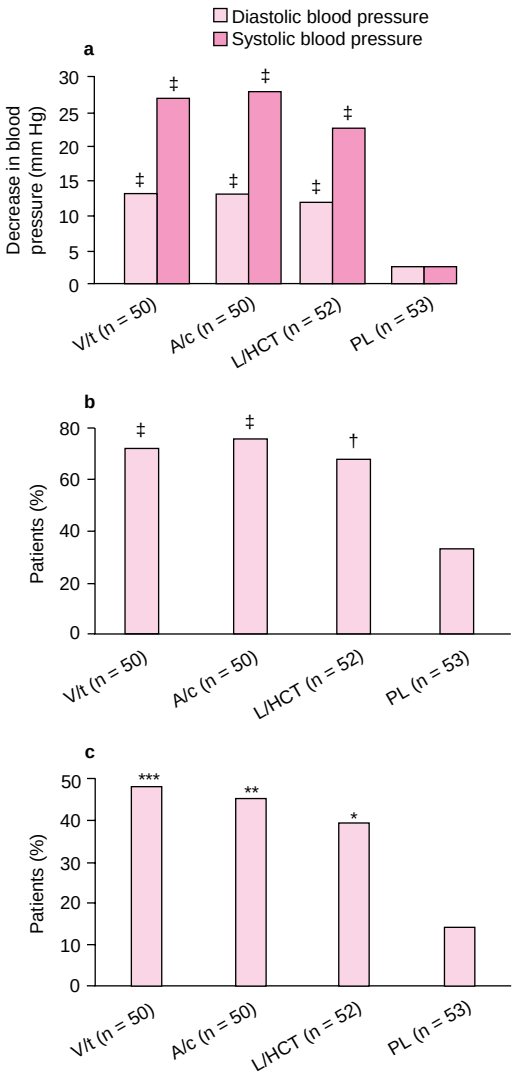


Fig. 1. Effects of verapamil SR/trandolapril versus other combination products on blood pressure in mild to moderate hypertension. Effects of sustained-release verapamil/trandolapril (V/t) 180/2mg once daily for 8 weeks on (a) sitting diastolic and systolic blood pressures, (b) response to treatment and (c) normalisation of blood pressure in comparison with atenolol/chlorthalidone (A/c) 100/25mg, lisinopril/hydrochlorothiazide (L/HCT) 20/12.5mg and placebo (PL) administered once daily for 8 weeks to 205 patients with mild to moderate essential hypertension; results from a randomised, double-blind study.[9] * $p < 0.005$, ** $p < 0.002$, *** $p < 0.0005$, † $p < 0.0002$, ‡ $p < 0.0001$ *vs* placebo.

mg/day (by about 9 and 5mm Hg, respectively). However, response rates (defined as a supine DBP of <90mm Hg or a reduction of ≥10mm Hg) did not differ significantly between treatment groups.[12]

- The addition of hydrochlorothiazide to verapamil SR/trandolapril decreased DBP and SBP to a greater extent than verapamil SR/trandolapril (by 19 and 27mm Hg from baseline, respectively, $p < 0.001$ *vs* verapamil SR/trandolapril).[12]

- When results from Black and White patients were evaluated separately, generally no significant differences were observed in blood pressure reductions or response rates between the 2 subgroups. However, monotherapy with trandolapril significantly reduced SBP relative to baseline values in White (by 7.5mm Hg, $p < 0.001$), but not Black (by 1.2mm Hg), patients.[12]

- In a nonblind, noncomparative trial in 21 Black patients with mild to moderate hypertension which, in most cases, had not been controlled by previous antihypertensive therapy, verapamil SR/trandolapril (180/2 to 360/4mg once daily or 360/4mg plus hydrochlorothiazide 12.5mg, titrated according to response, once daily for 16 weeks) significantly reduced mean 24-hour ambulatory blood pressure (from 150/96 at baseline to 131/82mm Hg, $p < 0.0001$). Similar results were observed in the 12-hour daytime or night-time SBP and DBP measurements. The addition of hydrochlorothiazide was needed in 2 patients.[24]

- A response rate (defined as a reduction in mean 24-hour or mean daytime DBP by >10mm Hg) was observed in 71% of patients; 76% of patients achieved a mean 24-hour DBP of <90mm Hg.[24]

- In a placebo-controlled trial involving 625 patients[11] and in 1 trial in 278 patients with no placebo control,[13] verapamil SR/trandolapril 240/4mg[11] and 180/2mg,[13] once daily for 6 or 8 weeks reduced sitting DBP and SBP to a significantly greater extent than monotherapy with the individual components (fig. 2a and b). This was not observed in another placebo-controlled trial after verapamil SR/trandolapril 180/1mg once daily for 8 weeks in 234 patients.[14]

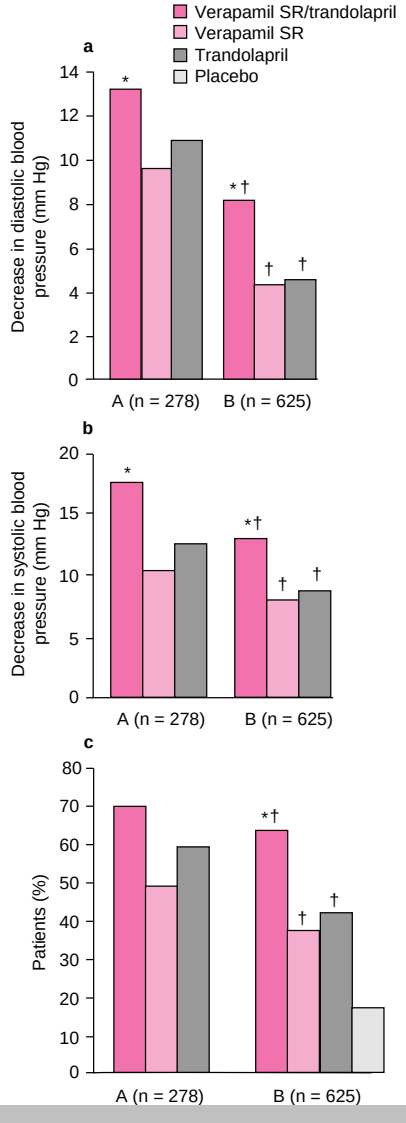


Fig. 2. Effects of verapamil SR/trandolapril versus the individual components on blood pressure in mild to moderate hypertension. Effects of sustained-release verapamil/trandolapril (180/2[13] or 240/4mg[11] once daily for 6 or 8 weeks) on (a) sitting diastolic and (b) sitting systolic blood pressure and (c) response rates in comparison with the individual components in patients with mild to moderate essential hypertension; results from randomised, double-blind studies. A = Viskoper et al.[13]; B = Messerli et al.[11]; * $p \leq 0.01$ *vs* monotherapy; † $p \leq 0.05$ *vs* placebo. Note: in the placebo-controlled trial, decreases in blood pressure in placebo recipients were not provided and values reported for active treatments may be adjusted for placebo.[11]

• In 2 studies, 24-hour ambulatory blood pressure was also measured.[13,14] Verapamil SR/trandolapril 180/1mg once daily reduced DBP to a greater extent than trandolapril 1mg once daily and verapamil 180mg once daily but the reduction in SBP was greater relative only to verapamil monotherapy.[14]

• In a separate analysis of 90 patients from the nonplacebo-controlled trial[13] who had a DBP <100mm Hg, DBP and SBP reductions over a 24-hour ambulatory period were significantly greater after verapamil SR/trandolapril 180/2mg once daily than after verapamil 180mg once daily or trandolapril 2mg once daily.[25]

• Response rates were significantly higher after verapamil SR/trandolapril 240/4 mg/day than after verapamil 240 mg/day or trandolapril 4 mg/day in the large study (fig. 2c).[11] Differences observed between combination therapy and monotherapy in normalisation rates or response rates in the other study were not statistically significant (fig. 2c).[13]

Congestive Heart Failure After Myocardial Infarction

• Cardiac events occurred less frequently after verapamil SR/trandolapril (240/1 mg/day for 1 month then 360/2 mg/day for 2 months) than after monotherapy with trandolapril (1 mg/day for 1 month then 2 mg/day for 2 months) in a double-blind, randomised trial of 100 post-acute myocardial infarction patients with congestive heart failure. All patients received diuretics throughout the study period and the use of aspirin, long-acting nitrates and digoxin was also permitted.[26]

• A combined cardiac event (defined as death, reinfarction, unstable angina or readmission due to worsening congestive heart failure) occurred in significantly fewer verapamil SR/trandolapril than trandolapril recipients (14 *vs* 35%, respectively, $p = 0.01$). Reinfarction was also less frequent in verapamil SR/trandolapril recipients than patients receiving trandolapril (2 *vs* 14%, $p < 0.03$). No significant difference was observed between the 2

treatment groups in the incidence of other individual events.[26,27]

Hypertension and Concomitant Coronary Artery Disease

• The INVEST trial (International Verapamil SR/Trandolapril) is under way to compare the efficacy of verapamil with or without trandolapril and hydrochlorothiazide with that of atenolol with or without hydrochlorothiazide and trandolapril in 27 000 patients with hypertension and coronary artery disease. The primary goal of this trial is to determine the comparative efficacy of the 2 regimens in preventing death or a major cardiovascular event (myocardial infarction or stroke). The comparative effects on blood pressure and anginal pain, as well as tolerability and safety issues, will also be examined.[28]

4. Tolerability

• No new adverse events have been reported after verapamil SR/trandolapril. Thus, the tolerability profile of verapamil SR/trandolapril is assumed to be consistent with that of the individual components.[29,30]

• In comparative trials involving 205 to 625 patients with mild to moderate essential hypertension (see section 3 and figures for study details), the incidence of adverse events after verapamil SR/trandolapril 180/1,[14] 180/2[9,13] or 240/4mg[11] once daily was similar to that after verapamil 180 or 240mg once daily, trandolapril 1 to 4mg once daily, atenolol/chlorthalidone 100/25mg once daily and lisinopril/hydrochlorothiazide 20/12.5mg once daily.

• The incidence of adverse events after verapamil SR/trandolapril ranged from 17 to 46% and was similar to that seen with placebo.[9,11] Constipation, cough, asthenia and headache were the most commonly reported adverse events after verapamil SR/trandolapril.[9,11,13,14,30] The manufacturer also reports dizziness, nausea and first-degree AV block.[29]

• In general, verapamil SR/trandolapril had no clinically significant effect on laboratory parameters.[9,13]

5. Verapamil SR/Trandolapril: Current Status

Verapamil SR/trandolapril is a fixed combination product which is widely available for the management of essential hypertension. It has shown clinical efficacy in patients with mild to severe essential hypertension which is similar to that of atenolol/chlorthalidone and lisinopril/hydrochlorothiazide, at least as good as metoprolol/hydrochlorothiazide and better than that of monotherapy with verapamil or trandolapril. Verapamil SR/ trandolapril may reduce the incidence of cardiac events relative to trandolapril in post-myocardial infarction patients with congestive heart failure.

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