

also contains corn starch, croscarmellose sodium, hypromellose, iron oxide, lactose monohydrate, povidone, sodium stearyl fumarate.

CLINICAL PHARMACOLOGY

Mechanism of Action

Trandolapril is deesterified to the diacid metabolite, trandolaprilat, which is approximately eight times more active as an inhibitor of ACE activity. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor, angiotensin II. Angiotensin II is a potent peripheral vasoconstrictor that also stimulates secretion of aldosterone by the adrenal cortex and provides negative feedback for renin secretion. The effect of trandolapril in hypertension appears to result primarily from the inhibition of circulating and tissue ACE activity thereby reducing angiotensin II formation, decreasing vasoconstriction, decreasing aldosterone secretion, and increasing plasma renin. Decreased aldosterone secretion leads to diuresis, natriuresis, and a small increase of serum potassium. In controlled clinical trials, treatment with MAVIK alone resulted in mean increases in potassium of 0.1 mEq/L. (See **PRECAUTIONS.**)

ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent peptide vasodilator; whether increased levels of bradykinin play a role in the therapeutic effect of trandolapril remains to be elucidated.

While the principal mechanism of antihypertensive effect is thought to be through the renin-angiotensin-aldosterone system, trandolapril exerts antihypertensive actions even in patients with low-renin hypertension. MAVIK was an effective antihypertensive in all races studied. Both black patients (usually a predominantly low-renin group) and non-black patients responded to 2 to 4 mg of MAVIK.

Pharmacokinetics and Metabolism

Pharmacokinetics

Trandolapril's ACE-inhibiting activity is primarily due to its diacid metabolite, trandolaprilat. Cleavage of the ester group of trandolapril, primarily in the liver, is responsible for conversion. Absolute bioavailability after oral administration of trandolapril is about 10% as trandolapril and 70% as trandolaprilat. After oral trandolapril under fasting conditions, peak trandolapril levels occur at about one hour and peak trandolaprilat levels occur between 4 and 10 hours. The elimination half-life of trandolapril is about 6 hours. At steady state, the effective half-life of trandolaprilat is 22.5 hours. Like all ACE inhibitors, trandolaprilat also has a prolonged terminal elimination phase, involving a small fraction of administered drug, probably representing binding to plasma and tissue ACE. During multiple dosing of trandolapril, there is no significant accumulation of trandolaprilat. Food slows absorption of trandolapril, but does not affect AUC or C_{max} of trandolaprilat or C_{max} of trandolapril.

Metabolism and Excretion

After oral administration of trandolapril, about 33% of parent drug and metabolites are recovered in urine, mostly as trandolaprilat, with about 66% in feces. The extent of the absorbed dose which is biliary excreted

has not been determined. Plasma concentrations (C_{\max} and AUC of trandolapril and C_{\max} of trandolaprilat) are dose proportional over the 1-4 mg range, but the AUC of trandolaprilat is somewhat less than dose proportional. In addition to trandolaprilat, at least 7 other metabolites have been found, principally glucuronides or deesterification products.

Serum protein binding of trandolapril is about 80%, and is independent of concentration. Binding of trandolaprilat is concentration-dependent, varying from 65% at 1000 ng/mL to 94% at 0.1 ng/mL, indicating saturation of binding with increasing concentration.

The volume of distribution of trandolapril is about 18 liters. Total plasma clearances of trandolapril and trandolaprilat after approximately 2 mg IV doses are about 52 liters/hour and 7 liters/hour respectively. Renal clearance of trandolaprilat varies from 1-4 liters/hour, depending on dose.

Special Populations

Pediatric

Trandolapril pharmacokinetics have not been evaluated in patients < 18 years of age.

Geriatric and Gender

Trandolapril pharmacokinetics have been investigated in the elderly (> 65 years) and in both genders. The plasma concentration of trandolapril is increased in elderly hypertensive patients, but the plasma concentration of trandolaprilat and inhibition of ACE activity are similar in elderly and young hypertensive patients. The pharmacokinetics of trandolapril and trandolaprilat and inhibition of ACE activity are similar in male and female elderly hypertensive patients.

Race

Pharmacokinetic differences have not been evaluated in different races.

Renal Insufficiency

Compared to normal subjects, the plasma concentrations of trandolapril and trandolaprilat are approximately 2-fold greater and renal clearance is reduced by about 85% in patients with creatinine clearance below 30 ml/min and in patients on hemodialysis. Dosage adjustment is recommended in renally impaired patients. (See **DOSAGE AND ADMINISTRATION**.)

Hepatic Insufficiency

Following oral administration in patients with mild to moderate alcoholic cirrhosis, plasma concentrations of trandolapril and trandolaprilat were, respectively, 9-fold and 2-fold greater than in normal subjects, but inhibition of ACE activity was not affected. Lower doses should be considered in patients with hepatic insufficiency. (See **DOSAGE AND ADMINISTRATION**.)

Drug Interactions

Trandolapril did not affect the plasma concentration (pre-dose and 2 hours post-dose) of oral digoxin (0.25 mg). Coadministration of trandolapril and cimetidine led to an increase of about 44% in C_{max} for trandolapril, but no difference in the pharmacokinetics of trandolaprilat or in ACE inhibition. Coadministration of trandolapril and furosemide led to an increase of about 25% in the renal clearance of trandolaprilat, but no effect was seen on the pharmacokinetics of furosemide or trandolaprilat or on ACE inhibition.

Pharmacodynamics and Clinical Effects

A single 2-mg dose of MAVIK produces 70 to 85% inhibition of plasma ACE activity at 4 hours with about 10% decline at 24 hours and about half the effect manifest at 8 days. Maximum ACE inhibition is achieved with a plasma trandolaprilat concentration of 2 ng/mL. ACE inhibition is a function of trandolaprilat concentration, not trandolapril concentration. The effect of trandolapril on exogenous angiotensin I was not measured.

Hypertension

Four placebo-controlled dose response studies were conducted using once-daily oral dosing of MAVIK in doses from 0.25 to 16 mg per day in 827 black and non-black patients with mild to moderate hypertension. The minimal effective once-daily dose was 1 mg in non-black patients and 2 mg in black patients. Further decreases in trough supine diastolic blood pressure were obtained in non-black patients with higher doses, and no further response was seen with doses above 4 mg (up to 16 mg). The antihypertensive effect diminished somewhat at the end of the dosing interval, but trough/peak ratios are well above 50% for all effective doses. There was a slightly greater effect on the diastolic pressure, but no difference on systolic pressure with b.i.d. dosing. During chronic therapy, the maximum reduction in blood pressure with any dose is achieved within one week. Following 6 weeks of monotherapy in placebo-controlled trials in patients with mild to moderate hypertension, once-daily doses of 2 to 4 mg lowered supine or standing systolic/diastolic blood pressure 24 hours after dosing by an average 7-10/4-5 mmHg below placebo responses in non-black patients. Once-daily doses of 2 to 4 mg lowered blood pressure 4-6/3-4 mmHg in black patients. Trough to peak ratios for effective doses ranged from 0.5 to 0.9. There were no differences in response between men and women, but responses were somewhat greater in patients under 60 than in patients over 60 years old. Abrupt withdrawal of MAVIK has not been associated with a rapid increase in blood pressure.

Administration of MAVIK to patients with mild to moderate hypertension results in a reduction of supine, sitting and standing blood pressure to about the same extent without compensatory tachycardia.

Symptomatic hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted. (See **WARNINGS**.) Use of MAVIK in combination with thiazide diuretics gives a blood pressure lowering effect greater than that seen with either agent alone, and the additional effect of trandolapril is similar to the effect of monotherapy.

Heart Failure Post Myocardial Infarction or Left Ventricular Dysfunction Post Myocardial Infarction

The Trandolapril Cardiac Evaluation (TRACE) Trial was a Danish, 27-center, double-blind, placebo controlled, parallel-group study of the effect of trandolapril on all-cause mortality in stable patients with echocardiographic evidence of left ventricular dysfunction 3 to 7 days after a myocardial infarction. Subjects with residual ischemia or overt heart failure were included. Patients tolerant of a test dose of 1 mg trandolapril were randomized to placebo (n=873) or trandolapril (n=876) and followed for 24 months. Among patients randomized to trandolapril, who began treatment on 1 mg, 62% were successfully titrated to a target dose of 4 mg once daily over a period of weeks. The use of trandolapril was associated with a 16% reduction in the risk of all-cause mortality (p=0.042), largely cardiovascular mortality. Trandolapril was also associated with a 20% reduction in the risk of progression of heart failure (p=0.047), defined by a time-to-first-event analysis of death attributed to heart failure, hospitalization for heart failure, or requirement for open-label ACE inhibitor for the treatment of heart failure. There was no significant effect of treatment on other end-points: subsequent hospitalization, incidence of recurrent myocardial infarction, exercise tolerance, ventricular function, ventricular dimensions, or NYHA class.

The population in TRACE was entirely Caucasian and had less usage than would be typical in a U.S. population of other post-infarction interventions: 42% thrombolysis, 16% beta-adrenergic blockade, and 6.7% PTCA or CABG during the entire period of follow-up. Blood pressure control, especially in the placebo group, was poor: 47 to 53% of patients randomized to placebo and 32 to 40% of patients randomized to trandolapril had blood pressures > 140/95 at 90-day follow-up visits.

INDICATIONS AND USAGE

Hypertension

MAVIK is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medication such as hydrochlorothiazide.

Heart Failure Post Myocardial Infarction or Left-Ventricular Dysfunction Post Myocardial Infarction

MAVIK is indicated in stable patients who have evidence of left-ventricular systolic dysfunction (identified by wall motion abnormalities) or who are symptomatic from congestive heart failure within the first few days after sustaining acute myocardial infarction. Administration of trandolapril to Caucasian patients has been shown to decrease the risk of death (principally cardiovascular death) and to decrease the risk of heart failure-related hospitalization (see **CLINICAL PHARMACOLOGY - Heart Failure or Left-Ventricular Dysfunction Post Myocardial Infarction** for details of the survival trial).

CONTRAINDICATIONS

MAVIK is contraindicated in patients who are hypersensitive to this product, in patients with hereditary/idiopathic angioedema, and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors, including MAVIK, may be subject to a variety of adverse reactions, some of them serious.

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions did not occur when ACE inhibitors were temporarily withheld, but they reappeared when the ACE inhibitors were inadvertently readministered.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Head and Neck Angioedema

In controlled trials ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients. Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors including MAVIK. Symptoms suggestive of angioedema or facial edema occurred in 0.13% of MAVIK-treated patients. Two of the four cases were life-threatening and resolved without treatment or with medication (corticosteroids). Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with MAVIK should be discontinued immediately, the patient treated in accordance with accepted medical care and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms.

Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, emergency therapy, including but not limited to subcutaneous epinephrine solution 1:1,000 (0.3 to 0.5 mL) should be promptly administered. (See PRECAUTIONS - Information for Patients and ADVERSE REACTIONS.)

Intestinal Angioedema

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor.

Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Hypotension

MAVIK can cause symptomatic hypotension. Like other ACE inhibitors, MAVIK has only rarely been associated with symptomatic hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been salt- or volume-depleted as a result of prolonged treatment with diuretics, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating treatment with MAVIK. (See **PRECAUTIONS - Drug Interactions**, and **ADVERSE REACTIONS**.) In controlled and uncontrolled studies, hypotension was reported as an adverse event in 0.6% of patients and led to discontinuations in 0.1% of patients.

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia, and rarely, with acute renal failure and death. In such patients, MAVIK therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely during the first 2 weeks of treatment and, thereafter, whenever the dosage of MAVIK or diuretic is increased. (See **DOSAGE AND ADMINISTRATION**.) Care in avoiding hypotension should also be taken in patients with ischemic heart disease, aortic stenosis, or cerebrovascular disease.

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of MAVIK or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of trandolapril are insufficient to show that trandolapril does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen-vascular disease and/or renal disease should be considered.

Hepatic Failure

ACE inhibitors rarely have been associated with a syndrome of cholestatic jaundice, fulminant hepatic necrosis, and death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Fetal Toxicity

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue MAVIK as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue MAVIK, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to MAVIK for hypotension, oliguria, and hyperkalemia (See **PRECAUTIONS, Pediatric Use**).

Doses of 0.8 mg/kg/day (9.4 mg/m²/day) in rabbits, 1000 mg/kg/day (7000 mg/m²/day) in rats, and 25 mg/kg/day (295 mg/m²/day) in cynomolgus monkeys did not produce teratogenic effects. These doses represent 10 and 3 times (rabbits), 1250 and 2564 times (rats), and 312 and 108 times (monkeys) the maximum projected human dose of 4 mg based on body-weight and body-surface-area, respectively assuming a 50 kg woman.

PRECAUTIONS

General

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including MAVIK (trandolapril), may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

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Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACE inhibitors have been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or the ACE inhibitor may be required. **Evaluation of hypertensive patients should always include assessment of renal function.** (See **DOSAGE AND ADMINISTRATION.**)

Hyperkalemia and Potassium-sparing Diuretics

In clinical trials, hyperkalemia (serum potassium > 6.00 mEq/L) occurred in approximately 0.4% of hypertensive patients receiving MAVIK. In most cases, elevated serum potassium levels were isolated values, which resolved despite continued therapy. None of these patients were discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with MAVIK. (See **PRECAUTIONS - Drug Interactions.**)

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough. In controlled trials of trandolapril, cough was present in 2% of trandolapril patients and 0% of patients given placebo. There was no evidence of a relationship to dose.

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, MAVIK will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema

Angioedema, including laryngeal edema, may occur at any time during treatment with ACE inhibitors, including MAVIK. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician. (See **WARNINGS and ADVERSE REACTIONS.**)

Symptomatic Hypotension

Patients should be cautioned that light-headedness can occur, especially during the first days of MAVIK therapy, and should be reported to a physician. If actual syncope occurs, patients should be told to stop taking the drug until they have consulted with their physician (see **WARNINGS**.)

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting, resulting in reduced fluid volume, may precipitate an excessive fall in blood pressure with the same consequences of light-headedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor that has a long duration of action.

Hyperkalemia

Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician. (See **PRECAUTIONS**.)

Neutropenia

Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which could be a sign of neutropenia.

Pregnancy

Female patients of childbearing age should be told about the consequences of exposure to MAVIK during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with MAVIK is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant Diuretic Therapy

As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may experience an excessive reduction of blood pressure after initiation of therapy with MAVIK. The possibility of exacerbation of hypotensive effects with MAVIK may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with MAVIK. If it is not possible to discontinue the diuretic, the starting dose of trandolapril should be reduced. (See **DOSAGE AND ADMINISTRATION**.)

Agents Increasing Serum Potassium

Trandolapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. Use of potassium-sparing diuretics (spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes concomitantly with ACE inhibitors can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be used with caution and with appropriate monitoring of serum potassium. (See **PRECAUTIONS**.)

Antidiabetic Agents

Concomitant use of ACE inhibitors and antidiabetic medicines (insulin or oral hypoglycemic agents) may cause an increased blood glucose lowering effect with greater risk of hypoglycemia.

Lithium

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including trandolapril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving trandolapril and NSAID therapy.

The antihypertensive effect of ACE inhibitors, including trandolapril may be attenuated by NSAIDs.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including MAVIK.

Other

No clinically significant pharmacokinetic interaction has been found between trandolaprilat and food, cimetidine, digoxin, or furosemide.

The anticoagulant effect of warfarin was not significantly changed by trandolapril. As with all other inhibitors of RAS, NSAIDs may reduce the antihypertensive effects of trandolapril. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with trandolapril.

The hypotensive effect of certain inhalation anesthetics may be enhanced by ACE inhibitors including trandolapril (See **PRECAUTIONS-Surgery/Anesthesia.**)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted with oral trandolapril administered by gavage to mice (78 weeks) and rats (104 and 106 weeks). No evidence of carcinogenic potential was seen in mice dosed up to 25 mg/kg/day (85 mg/m²/day) or rats dosed up to 8 mg/kg/day (60 mg/m²/day). These doses are 313 and 32 times (mice), and 100 and 23 times (rats) the maximum recommended human daily dose (MRHDD) of 4 mg based on body-weight and body-surface-area, respectively assuming a 50 kg individual. The genotoxic potential of trandolapril was evaluated in the microbial mutagenicity (Ames) test, the point mutation and chromosome aberration assays in Chinese hamster V79 cells, and the micronucleus test in mice. There was no evidence of mutagenic or clastogenic potential in these *in vitro* and *in vivo* assays.

Reproduction studies in rats did not show any impairment of fertility at doses up to 100 mg/kg/day (710 mg/m²/day) of trandolapril, or 1250 and 260 times the MRHDD on the basis of body-weight and body-surface-area, respectively.

Nursing Mothers

Radiolabeled trandolapril or its metabolites are secreted in rat milk. MAVIK should not be administered to nursing mothers.

Geriatric Use

In placebo-controlled studies of MAVIK, 31.1% of patients were 60 years and older, 20.1% were 65 years and older, and 2.3% were 75 years and older. No overall differences in effectiveness or safety were observed between these patients and younger patients. (Greater sensitivity of some older individual patients cannot be ruled out).

Pediatric Use

Neonates with a history of *in utero* exposure to MAVIK:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

The safety and effectiveness of MAVIK in pediatric patients have not been established.

ADVERSE REACTIONS

The safety experience in U.S. placebo-controlled trials included 1069 hypertensive patients, of whom 832 received MAVIK. Nearly 200 hypertensive patients received MAVIK for over one year in open-label trials. In controlled trials, withdrawals for adverse events were 2.1% on placebo and 1.4% on MAVIK. Adverse events considered at least possibly related to treatment occurring in 1% of MAVIK-treated patients and more common on MAVIK than placebo, pooled for all doses, are shown below, together with the frequency of discontinuation of treatment because of these events.

ADVERSE EVENTS IN PLACEBO-CONTROLLED HYPERTENSION TRIALS

	Occurring at 1% or greater	
	MAVIK (N=832) % Incidence (% Discontinuance)	PLACEBO (N=237) % Incidence (% Discontinuance)
Cough	1.9 (0.1)	0.4 (0.4)
Dizziness	1.3 (0.2)	0.4 (0.4)
Diarrhea	1.0 (0.0)	0.4 (0.0)

Headache and fatigue were all seen in more than 1% of MAVIK-treated patients but were more frequently seen on placebo. Adverse events were not usually persistent or difficult to manage.

Left Ventricular Dysfunction Post Myocardial Infarction

Adverse reactions related to MAVIK occurring at a rate greater than that observed in placebo-treated patients with left ventricular dysfunction, are shown below. The incidences represent the experiences from the TRACE study. The follow-up time was between 24 and 50 months for this study.

Percentage of Patients with Adverse Events Greater Than Placebo

Adverse Event	Placebo-Controlled (TRACE) Mortality Study	
	Trandolapril N=876	Placebo N=873
Cough	35	22
Dizziness	23	17
Hypotension	11	6.8
Elevated serum uric acid	15	13
Elevated BUN	9.0	7.6
PICA or CABG	7.3	6.1
Dyspepsia	6.4	6.0
Syncope	5.9	3.3
Hyperkalemia	5.3	2.8
Bradycardia	4.7	4.4
Hypocalcemia	4.7	3.9
Myalgia	4.7	3.1
Elevated creatinine	4.7	2.4
Gastritis	4.2	3.6
Cardiogenic shock	3.8	< 2

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Intermittent claudication	3.8	< 2
Stroke	3.3	3.2
Asthenia	3.3	2.6

Clinical adverse experiences possibly or probably related or of uncertain relationship to therapy occurring in 0.3% to 1.0% (except as noted) of the patients treated with MAVIK (with or without concomitant calcium ion antagonist or diuretic) in controlled or uncontrolled trials (N=1134) and less frequent, clinically significant events seen in clinical trials or post-marketing experience include (listed by body system):

General Body Function

Chest pain.

Cardiovascular

AV first degree block, bradycardia, edema, flushing, , palpitations.

Central Nervous System

Drowsiness, insomnia, paresthesia, vertigo.

Dermatologic

Pruritus, pemphigus.

Eye, Ear, Nose, Throat

Epistaxis, throat inflammation, upper respiratory tract infection.

Emotional, Mental, Sexual States

Anxiety, impotence, decreased libido.

Gastrointestinal

Abdominal distention, abdominal pain/cramps, constipation, dyspepsia, diarrhea, vomiting, nausea.

Hemopoietic

Decreased leukocytes, decreased neutrophils.

Metabolism and Endocrine

Increased liver enzymes including SGPT (ALT).

Musculoskeletal System

Extremity pain, muscle cramps, gout.

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Pulmonary

Dyspnea

Postmarketing

The following adverse reactions were identified during post approval use of MAVIK. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General Body Function

Malaise, fever.

Cardiovascular

Myocardial infarction, myocardial ischemia, angina pectoris, cardiac failure, ventricular tachycardia, tachycardia, transient ischemic attack, arrhythmia.

Central Nervous System

Cerebral hemorrhage.

Dermatologic

Alopecia, sweating, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Emotional, Mental, Sexual States

Hallucination, depression.

Gastrointestinal

Dry mouth, pancreatitis, jaundice and hepatitis.

Hemopoietic

Agranulocytosis, pancytopenia.

Metabolism and Endocrine

Increased SGOT (AST).

Pulmonary

Bronchitis.

Renal and Urinary

Renal failure.

Clinical Laboratory Test Findings

Hematology

(Thrombocytopenia.

Serum Electrolytes

Hyponatremia.

Creatinine and Blood Urea Nitrogen

Increases in creatinine levels occurred in 1.1% of patients receiving MAVIK alone and 7.3% of patients treated with MAVIK, a calcium ion antagonist and a diuretic. Increases in blood urea nitrogen levels occurred in 0.6% of patients receiving MAVIK alone and 1.4% of patients receiving MAVIK, a calcium ion antagonist, and a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See **PRECAUTIONS** and **WARNINGS**.)

Liver Function Tests

Occasional elevation of transaminases at the rate of 3X upper normals occurred in 0.8% of patients and persistent increase in bilirubin occurred in 0.2% of patients. Discontinuation for elevated liver enzymes occurred in 0.2% of patients.

Other

Another potentially important adverse experience, eosinophilic pneumonitis, has been attributed to other ACE inhibitors.

OVERDOSAGE

No data are available with respect to overdosage in humans. The oral LD₅₀ of trandolapril in mice was 4875 mg/Kg in males and 3990 mg/Kg in females. In rats, an oral dose of 5000 mg/Kg caused low mortality (1 male out of 5; 0 females). In dogs, an oral dose of 1000 mg/Kg did not cause mortality and abnormal clinical signs

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were not observed. In humans the most likely clinical manifestation would be symptoms attributable to severe hypotension. Symptoms also expected with ACE inhibitors hypotension, hyperkalemia, and renal failure.

Laboratory determinations of serum levels oftrandolapril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management oftrandolapril overdose. No data are available to suggest that physiological maneuvers (e.g., maneuvers to change the pH of the urine) might accelerate elimination oftrandolapril and its metabolites. Trandolaprilat is removed by hemodialysis.

Angiotensin II could presumably serve as a specific antagonist antidote in the setting oftrandolapril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect oftrandolapril is achieved through vasodilation and effective hypovolemia, it is reasonable to treattrandolapril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

Hypertension

The recommended initial dosage of MAVIK for patients not receiving a diuretic is 1 mg once daily in non-black patients and 2 mg in black patients. Dosage should be adjusted according to the blood pressure response. Generally, dosage adjustments should be made at intervals of at least 1 week. Most patients have required dosages of 2 to 4 mg once daily. There is little clinical experience with doses above 8 mg.

Patients inadequately treated with once-daily dosing at 4 mg may be treated with twice-daily dosing. If blood pressure is not adequately controlled with MAVIK monotherapy, a diuretic may be added.

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of MAVIK. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with MAVIK. (See **WARNINGS**.) Then, if blood pressure is not controlled with MAVIK alone, diuretic therapy should be resumed. If the diuretic cannot be discontinued, an initial dose of 0.5 mg MAVIK should be used with careful medical supervision for several hours until blood pressure has stabilized. The dosage should subsequently be titrated (as described above) to the optimal response. (See **WARNINGS**, **PRECAUTIONS**, and **DRUG INTERACTIONS**.)

Concomitant administration of MAVIK with potassium supplements, potassium salt substitutes, or potassium sparing diuretics can lead to increases of serum potassium. (See **PRECAUTIONS**.)

Heart Failure Post Myocardial Infarction or Left-Ventricular Dysfunction Post Myocardial Infarction

The recommended starting dose is 1 mg, once daily. Following the initial dose, all patients should be titrated (as tolerated) toward a target dose of 4 mg, once daily. If a 4 mg dose is not tolerated, patients can continue therapy with the greatest tolerated dose.

Dosage Adjustment in Renal Impairment or Hepatic Cirrhosis

For patients with a creatinine clearance < 30 mL/min. or with hepatic cirrhosis, the recommended starting dose, based on clinical and pharmacokinetic data, is 0.5 mg daily. Patients should subsequently have their dosage titrated (as described above) to the optimal response.

HOW SUPPLIED

MAVIK (trandolapril tablets) are supplied as follows:

1 mg tablet - Salmon colored, round shaped, scored, compressed tablets, with **Abbott “A” logo** on one side and Abbo-Code identification letters FT on the other side. NDC 0074-2278-13 - bottles of 100 NDC 0074-2278-11 - unit dose packs of 100

2 mg tablet - Yellow colored, round shaped, compressed tablets, with **Abbott “A” logo** on one side and Abbo-Code identification letters FX on the other side. NDC 0074-2279-13 - bottles of 100 NDC 0074-2279-11 - unit dose packs of 100

4 mg tablet - Rose colored, round shaped, compressed tablets, with **Abbott “A” logo** on one side and Abbo-Code identification letters FZ on the other side. NDC 0074-2280-13 - bottles of 100 NDC 0074-2280-11 - unit dose packs of 100

Dispense in well-closed container with safety closure.

Storage

Store at controlled room temperature: 20-25°C (68-77°F) see USP.

Manufactured by

Halo Pharmaceutical Inc.

Whippany, N.J. 07981, U.S.A.

for

Abbott Laboratories

North Chicago, IL 60064, U.S.A.

Revised: 12/2011

Dn2440v1-redlined-mavik-2011-dec-2

TARKA®

(trandolapril/verapamil hydrochloride ER tablets)

WARNING: FETAL TOXICITY

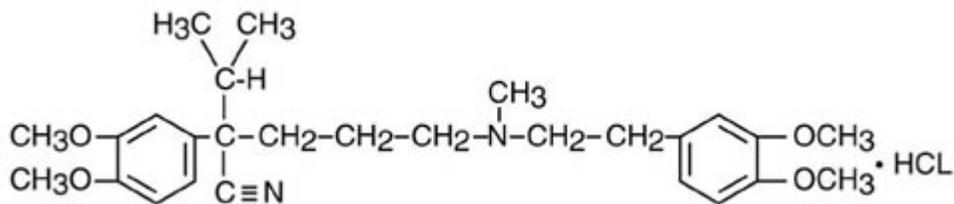
- When pregnancy is detected, discontinue TARKA as soon as possible.
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (see WARNINGS: Fetal Toxicity).

DESCRIPTION

TARKA (trandolapril/verapamil hydrochloride ER) combines a slow release formulation of a calcium channel blocker, verapamil hydrochloride, and an immediate release formulation of an angiotensin converting enzyme inhibitor, trandolapril.

Verapamil Component

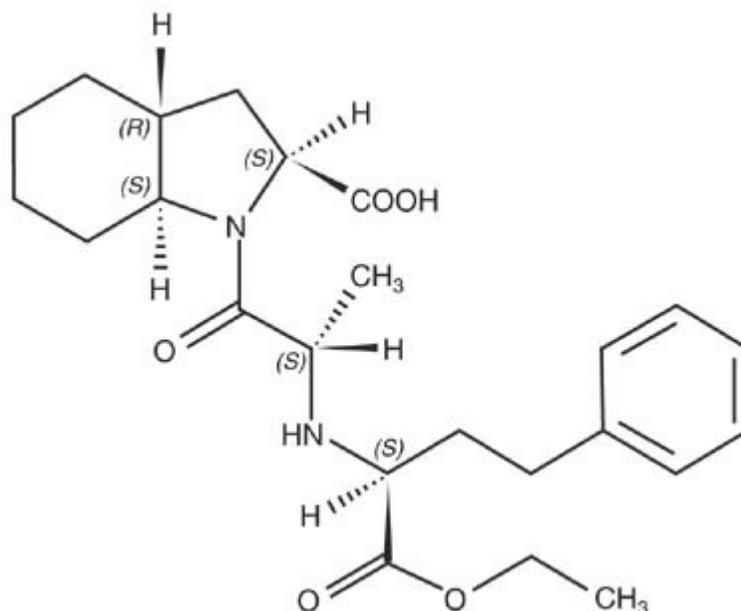
Verapamil hydrochloride is chemically described as benzeneacetonitrile, α [3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3, 4-dimethoxy- α -(1-methylethyl) hydrochloride. Its empirical formula is $C_{27}H_{38}N_2O_4 \cdot HCl$ and its structural formula is:



Verapamil hydrochloride is an almost white crystalline powder, with a molecular weight of 491.08. It is soluble in water, chloroform, and methanol. It is practically free of odor, with a bitter taste.

Trandolapril Component

Trandolapril is the ethyl ester prodrug of a nonsulfhydryl angiotensin converting enzyme (ACE) inhibitor, trandolaprilat. It is chemically described as (2S,3aR,7aS)-1-[(S)-N-[(S)-1-Carboxy-3-phenylpropyl]alanyl]hexahydro-2-indolinecarboxylic acid, 1-ethyl ester. Its empirical formula is $C_{24}H_{34}N_2O_5$ and its structural formula is:



Trandolapril is a white or almost white powder with a molecular weight of 430.54. It is soluble (>100 mg/mL) in chloroform, dichloromethane, and methanol.

TARKA tablets are formulated for oral administration, containing verapamil hydrochloride as a controlled release formulation and trandolapril as an immediate release formulation. The tablet strengths are trandolapril 2 mg/verapamil hydrochloride ER 180 mg, trandolapril 1 mg/verapamil hydrochloride ER 240 mg, trandolapril 2 mg/verapamil hydrochloride ER 240 mg, and trandolapril 4 mg/verapamil hydrochloride ER 240 mg. The tablets also contain the following ingredients: corn starch, dioctyl sodium sulfosuccinate, ethanol, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, purified water, silicon dioxide, sodium alginate, sodium stearyl fumarate, synthetic iron oxides, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Verapamil hydrochloride and trandolapril have been used individually and in combination for the treatment of hypertension. For the four dosing strengths, the antihypertensive effect of the combination is approximately additive to the individual components.

Verapamil Component

Verapamil is a calcium channel blocker that exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells. Verapamil exerts antihypertensive effects by decreasing systemic vascular resistance, usually without orthostatic decreases in blood pressure or reflex tachycardia. During isometric or dynamic exercise, verapamil does not alter systolic cardiac function in patients with normal ventricular function. Verapamil does not alter total serum calcium levels.

Trandolapril Component

Trandolapril is de-esterified to its diacid metabolite, trandolaprilat. Both inhibit angiotensin-converting enzyme (ACE) in human subjects and in animals. Trandolaprilat is about 8 times more potent than trandolapril. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex.

Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In controlled clinical trials, treatment with TARKA resulted in mean increases in potassium of 0.1 mEq/L (see **PRECAUTIONS**). Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA).

ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effect of TARKA remains to be elucidated.

While the mechanism through which trandolapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, trandolapril has an antihypertensive effect even in patients with low renin hypertension. Trandolapril is an effective antihypertensive in all races studied. Both black patients (usually a predominantly low renin group) and non-black patients respond to 2 to 4 mg of trandolapril.

Pharmacokinetics and Metabolism

TARKA

Following a single oral dose of TARKA in healthy subjects, peak plasma concentrations are reached within 0.5-2 hours for trandolapril and within 4-15 hours for verapamil. Peak plasma concentrations of the active desmethyl metabolite of verapamil, norverapamil, are reached within 5-15 hours. Cleavage of the ester group converts trandolapril to its active diacid metabolite, trandolaprilat, which reaches peak plasma concentrations within 2-12 hours. The pharmacokinetics of trandolapril and trandolaprilat are not altered when trandolapril is administered in combination with verapamil, compared to monotherapy.

The AUC and C_{max} for both verapamil and norverapamil are increased when 240 mg of controlled release verapamil is administered concomitantly with 4 mg trandolapril. The increase in C_{max} is 54 and 30% and the AUC is increased by 65 and 32% for verapamil and norverapamil, respectively. Administration of TARKA 4/240 (4 mg trandolapril and 240 mg verapamil hydrochloride ER) with a high-fat meal does not alter the bioavailability of trandolapril whereas verapamil peak concentrations and area under the curve (AUC) decrease 37% and 28%, respectively. Food thus decreases verapamil bioavailability and the time to peak plasma concentration for both verapamil and norverapamil are delayed by approximately 7 hours. Both optical isomers of verapamil are similarly affected.

The elimination half life of trandolapril is about 6 hours. At steady state, the effective half-life of trandolaprilat is 22.5 hours. Like all ACE inhibitors, trandolaprilat also has a prolonged terminal elimination

phase, involving a small fraction of administered drug, probably representing binding to plasma and tissue ACE.

The terminal half-life of verapamil is 6-11 hours. Steady-state plasma concentrations of the two components are achieved after about a week of once-daily dosing of TARKA. At steady-state, plasma concentrations of verapamil and trandolaprilat are up to two-fold higher than those observed after a single oral TARKA dose.

The pharmacokinetics of verapamil and trandolaprilat are significantly different in the elderly (≥ 65 years) than in younger subjects. The bioavailability of verapamil and norverapamil are increased by 87% and 77%, respectively, and that of trandolapril by approximately 35% in the elderly. AUCs are approximately 80% and 35% higher, respectively.

Verapamil Component

With the immediate release formulation, more than 90% of the orally administered dose is absorbed with peak plasma concentrations of verapamil observed 1 to 2 hours after dosing. A delayed rate but similar extent of absorption is observed for the sustained release formulation when compared to the immediate release formulation. Because of the rapid biotransformation of verapamil during its first pass through the portal circulation, absolute bioavailability ranges from 20% to 35%. A nonlinear correlation exists between verapamil dose and plasma concentrations.

In early dose titration with verapamil, a relationship exists between plasma concentrations of verapamil and prolongation of the PR interval. However, during chronic administration, this relationship may disappear. No relationship has been established between the plasma concentration of verapamil and reduction in blood pressure.

In healthy subjects, orally administered verapamil undergoes extensive metabolism in the liver. Twelve metabolites have been identified in plasma; all except norverapamil are present in trace amounts only. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. Urinary excretion of unchanged drug is about 3% to 4% of the dose. Verapamil is approximately 90% bound to plasma proteins.

In patients with hepatic insufficiency, verapamil clearance is decreased about 30% and the elimination half-life is prolonged up to 14 to 16 hours (see **PRECAUTIONS**). In patients with liver dysfunction, a dosage adjustment may be required. In the elderly (≥ 65 years), verapamil clearance is reduced resulting in increases in elimination half-life.

Trandolapril Component

Following oral administration of trandolapril, the absolute bioavailability of trandolapril is approximately 10% as trandolapril and 70% as trandolaprilat. Plasma concentrations of trandolaprilat but not trandolapril increase in proportion with dose. Plasma concentrations of trandolaprilat decline in a triphasic manner. The more prolonged terminal elimination phase probably represents a small fraction of dose saturably bound to ACE.

After an oral radiolabeled dose of trandolapril, excretion of trandolapril and metabolites account for 33% of the dose in the urine and about 66% in the feces. Less than 1% of the dose is excreted in the urine as unchanged drug. Serum protein binding of trandolapril is about 80%, and is independent of concentration. Binding of trandolaprilat is concentration-dependent, varying from 65% at 1000 ng/mL to 94% at 0.1 ng/mL, indicating saturation of binding with increasing concentration.

Compared to normal subjects, the plasma concentrations of trandolapril and trandolaprilat are approximately 2-fold greater and renal clearance is reduced by about 85% in patients with creatinine clearance below 30 mL/min and in patients on hemodialysis. Dosage adjustment is recommended in renally impaired patients (see **DOSAGE AND ADMINISTRATION**).

Following oral administration in patients with mild to moderate alcoholic cirrhosis, plasma concentrations of trandolapril and trandolaprilat were, respectively, 9-fold and 2-fold greater than in normal subjects, but inhibition of ACE activity was not affected. Lower doses should be considered in patients with hepatic insufficiency (see **DOSAGE AND ADMINISTRATION**).

Pharmacodynamics

TARKA

Verapamil does not interfere with ACE inhibition by trandolapril. Trandolapril does not alter the effect of verapamil on intra-cardiac conduction.

Verapamil Component

Verapamil dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm. This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of verapamil in vasospastic (Prinzmetal's or variant) as well as unstable angina at rest.

Verapamil regularly reduces the total systemic resistance (afterload) by dilating peripheral arterioles. By decreasing the influx of calcium, verapamil prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner.

Normal sinus rhythm is usually not affected, but in patients with sick sinus syndrome, verapamil may interfere with sinus node impulse generation and may induce sinus arrest or sinoatrial block. Atrioventricular block can occur in patients without preexisting conduction defects (see **WARNINGS**).

Verapamil does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization and conduction in depressed atrial fibers. Verapamil may shorten the antegrade effective refractory period of accessory bypass tracts. Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

Hemodynamics and Myocardial Metabolism: Verapamil reduces afterload and myocardial contractility. Improved left ventricular diastolic function in patients with idiopathic hypertrophic subaortic stenosis (IHSS) and those with coronary heart disease has also been observed with verapamil therapy. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil is countered by a reduction of afterload and cardiac index is usually not reduced. However, in patients with severe left ventricular dysfunction (e.g., pulmonary wedge pressure about 20 mmHg or ejection fraction less than 30%), or in patients taking beta-adrenergic blocking agents or other cardio-depressant drugs, deterioration of ventricular function may occur (see **DRUG INTERACTIONS**).

Pulmonary Function: Verapamil does not induce bronchoconstriction and hence, does not impair ventilatory function.

Trandolapril Component

After a single 2 mg dose of trandolapril, inhibition of ACE activity reaches a maximum (70-85%) at 4 hours with about 10% decline at 24 hours. Eight days after dosing, ACE inhibition is still 40%.

Four placebo-controlled dose response studies were conducted using once daily oral dosing of trandolapril in doses from 0.25 to 16 mg per day in 827 black and non-black patients with mild to moderate hypertension. The minimal effective once daily dose was 1.0 mg in non-black patients and 2.0 mg in black patients. Further decreases in trough supine diastolic blood pressure were obtained in non-black patients with higher doses, and no further response was seen with doses above 4 mg (up to 16 mg). The antihypertensive effect diminished somewhat at the end of the dosing interval.

During chronic therapy, the maximum reduction in blood pressure with any dose is achieved within one week. Following 6 weeks of monotherapy in placebo-controlled trials in patients with mild to moderate hypertension, once daily doses of 2 to 4 mg lowered supine or standing systolic/diastolic blood pressure 24 hours after dosing by an average 7-10/4-5 mmHg below placebo responses in non-black patients. Once daily doses of 2 to 4 mg lowered blood pressures 4-6/3-4 mmHg below placebo responses in black patients.

CLINICAL STUDIES

In controlled clinical trials, once daily doses of TARKA, trandolapril 4 mg/verapamil HCl ER 240 mg or trandolapril 2 mg/verapamil HCl ER 180 mg, decreased placebo-corrected seated pressure (systolic/diastolic) 24 hours after dosing by about 7-12/6-8 mmHg. Each of the components of TARKA added to the antihypertensive effect. Treatment effects were consistent across age groups (<65, ≥65 years), and gender (male, female).

Blood pressure reductions were significantly greater for the TARKA 4/240 combination than for either of the components used alone.

The antihypertensive effects of TARKA have continued during therapy for at least 1 year.

INDICATIONS AND USAGE

TARKA is indicated for the treatment of hypertension.

This fixed combination drug is not indicated for the initial therapy of hypertension (see DOSAGE and ADMINISTRATION).

In using TARKA, consideration should be given to the fact that an angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that trandolapril does not have similar risk (see **WARNINGS -Neutropenia/Agranulocytosis**).

CONTRAINDICATIONS

TARKA is contraindicated in patients who are hypersensitive to any ACE inhibitor or verapamil.

Because of the verapamil component, TARKA is contraindicated in:

1. Severe left ventricular dysfunction (see **WARNINGS**).
2. Hypotension (systolic pressure less than 90 mmHg) or cardiogenic shock.
3. Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker).
4. Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker).
5. Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes) (see **WARNINGS**).

Because of the trandolapril component, TARKA is contraindicated in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme (ACE) inhibitor.

WARNINGS

Heart Failure

Verapamil Component

Verapamil has a negative inotropic effect which, in most patients, is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. In clinical experience with 4,954 patients, 87 (1.8%) developed congestive heart failure or pulmonary edema. Verapamil should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction less than 30%, pulmonary wedge pressure above 20 mmHg, or severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta adrenergic blocker (see **DRUG INTERACTIONS**). Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment (Note interactions with digoxin under: **PRECAUTIONS**).

Trandolapril Component

Trandolapril, as an ACE inhibitor, may cause excessive hypotension in patients with congestive heart failure (see **WARNINGS - Hypotension**).

Hypotension

Verapamil Component

Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels which may result in dizziness or symptomatic hypotension.

Trandolapril Component

Trandolapril can cause symptomatic hypotension. Like other ACE inhibitors, trandolapril has only rarely been associated with symptomatic hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who are salt- or volume-depleted as a result of prolonged treatment with diuretics, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating treatment with trandolapril (see **PRECAUTIONS -Drug Interactions** and **ADVERSE REACTIONS**).

In controlled studies, hypotension was observed in 0.6% of patients receiving any combination of trandolapril and verapamil HCl ER.

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia, and, rarely, with acute renal failure and death (see **DOSAGE AND ADMINISTRATION**).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of verapamil HCl ER and/or trandolapril or reduced concomitant diuretic therapy should be considered.

Elevated Liver Enzymes/Hepatic Failure

Verapamil Component

Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even in the face of continued verapamil treatment. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge; half of these had clinical symptoms (malaise, fever, and/or right upper quadrant pain) in addition to elevations of SGOT, SGPT, and alkaline phosphatase.

Trandolapril Component

ACE inhibitors rarely have been associated with a syndrome of cholestatic jaundice, fulminant hepatic necrosis, and death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Liver abnormalities were noted in 3.2% of patients taking any of several combinations of trandolapril/verapamil doses. Periodic monitoring of liver function in patients taking TARKA is therefore prudent.

Accessory Bypass Tract (Wolff-Parkinson-White or Lown-Ganong-Levine Syndromes)

Verapamil Component

Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil (or digitalis). Although a risk of this occurring with oral verapamil has not been established, such patients receiving oral verapamil may be at risk and its use in these patients is contraindicated (see **CONTRAINDICATIONS**).

Treatment is usually DC-cardioversion. Cardioversion has been used safely and effectively after oral verapamil.

Atrioventricular Block

Verapamil Component

The effect of verapamil on AV conduction and the SA node may lead to asymptomatic first-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms. PR interval prolongation is correlated with verapamil plasma concentrations, especially during the early titration phases of therapy. Higher degrees of AV block, however, were infrequently (0.8%) observed. Marked first-degree block or progressive development to second- or third-degree AV block requires a reduction in dosage or, in rare instances, discontinuation of verapamil HCl and institution of appropriate therapy depending upon the clinical situation.

Patients with Hypertrophic Cardiomyopathy (IHSS)

Verapamil Component

In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects were seen. Three patients died in pulmonary edema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary edema and/or severe hypotension; abnormally high (over 20 mmHg) capillary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Sinus bradycardia occurred in 11% of the patients, second-degree AV

block in 4% and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction and only rarely did verapamil have to be discontinued.

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors, including trandolapril may be subject to a variety of adverse reactions, some of them serious.

Angioedema

Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors including trandolapril. Symptoms suggestive of angioedema or facial edema occurred in 0.13% of trandolapril-treated patients. Two of the four cases were life-threatening and resolved without treatment or with medication (corticosteroids). Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with TARKA should be discontinued immediately, the patient treated in accordance with accepted medical care and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, emergency therapy, including but not limited to subcutaneous epinephrine solution 1:1,000 (0.3 to 0.5 mL) should be promptly administered** (see **PRECAUTIONS** and **ADVERSE REACTIONS**).

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions did not occur when ACE inhibitors were temporarily withheld, but they reappeared when the ACE inhibitors were inadvertently readministered.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Neutropenia/Agranulocytosis

Trandolapril Component

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of trandolapril or TARKA are insufficient to show that trandolapril does not

cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen-vascular disease and/or renal disease should be considered.

Fetal Toxicity

Pregnancy Category D

Trandolapril Component

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue TARKA as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue TARKA, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to TARKA for hypotension, oliguria, and hyperkalemia (see **PRECAUTIONS, Pediatric Use**).

Doses of 0.8 mg/kg/day (9.4 mg/m²/day) in rabbits, 1000 mg/kg/day (7000 mg/m²/day) in rats, and 25 mg/kg/day (295 mg/m²/day) in cynomolgus monkeys did not produce teratogenic effects. These doses represent 10 and 3 times (rabbits), 1250 and 2564 times (rats), and 312 and 108 times (monkeys) the maximum projected human dose of 4 mg based on body-weight and body-surface-area, respectively assuming a 50 kg woman.

Trandolapril in doses of 0.8 mg/kg/day in rabbits, 100.0 mg/kg/day in rats, and 25 mg/kg/day in cynomolgus monkeys (10, 1250, and 312 times the maximum projected human dose, respectively, assuming a 50 kg woman) did not produce teratogenic effects.

PRECAUTIONS

Use in Patients with Impaired Hepatic Function

TARKA has not been evaluated in subjects with impaired hepatic function.

Verapamil Component

Since verapamil is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of immediate release verapamil to about 14 to 16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients.

Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see **OVERDOSAGE**) should be carried out.

Trandolapril Component

Trandolapril and trandolaprilat concentrations increase in patients with impaired liver function.

Use in Patients with Impaired Renal Function

TARKA has not been evaluated in patients with impaired renal function.

Verapamil Component

About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Verapamil is not removed by hemodialysis. Until further data are available, verapamil should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdose (see **OVERDOSAGE**).

Trandolapril Component

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including trandolapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACE inhibitors have been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or the ACE inhibitor may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Use in Patients with Attenuated (Decreased) Neuromuscular Transmission

Verapamil Component

It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission (see **PRECAUTIONS - Surgery/Anesthesia**).

Hyperkalemia and Potassium-sparing Diuretics

Trandolapril Component

In clinical trials, hyperkalemia (serum potassium > 6.00 mEq/L) occurred in approximately 0.4 percent of hypertensive patients receiving trandolapril and in 0.8% of patients receiving a dose of trandolapril (0.5-8 mg) in combination with a dose of verapamil SR (120-240 mg). In most cases, elevated serum potassium levels were isolated values, which resolved despite continued therapy. None of these patients were discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with trandolapril (see **PRECAUTIONS - Drug Interactions**).

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough. In controlled trials of trandolapril, cough was present in 2% of trandolapril patients and 0% of patients given placebo. There was no evidence of a relationship to dose.

Surgery/anesthesia

Trandolapril Component

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, trandolapril will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion (see **PRECAUTIONS - Use in Patients with Attenuated (Decreased) Neuromuscular Transmission**).

Drug Interactions

In vitro metabolic studies indicate that verapamil is metabolized by cytochrome P450 including CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Verapamil has been shown to be an inhibitor of CYP3A4 enzymes and P-glycoprotein (P-gp).

Clinically significant interactions have been reported with inhibitors of CYP3A4 (e.g. erythromycin, ritonavir) causing elevation of plasma levels of verapamil while inducers of CYP3A4 (e.g. rifampin) have caused a

lowering of plasma levels of verapamil. Therefore, patients receiving inhibitors or inducers of the cytochrome P450 system should be monitored for drug interactions.

Digitalis

Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. Chronic verapamil treatment can increase serum digoxin levels by 50 to 75% during the first week of therapy, and this can result in digoxin toxicity. In patients with hepatic cirrhosis, the influence of verapamil on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29%, respectively. Maintenance digoxin doses should be reduced when verapamil is administered, and the patient should be carefully monitored to avoid over- or under-digitalization. Whenever overdigitalization is suspected, the daily dose of digoxin should be reduced or temporarily discontinued. Upon discontinuation of any verapamil-containing regime including TARKA (trandolapril/verapamil hydrochloride ER), the patient should be reassessed to avoid underdigitalization. No clinically significant pharmacokinetic interaction has been found between trandolapril (or its metabolites) and digoxin.

Lithium

Verapamil Component

Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil-lithium therapy with either no change or an increase in serum lithium levels. Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. TARKA and lithium should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Clarithromycin

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent clarithromycin.

Erythromycin

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent erythromycin ethylsuccinate.

Cimetidine

The interaction between cimetidine and chronically administered verapamil has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged. No clinically significant pharmacokinetic interaction has been found between trandolapril (or its metabolites) and cimetidine.

Antiarrhythmic Agents

Verapamil Component

Disopyramide Phosphate

Data on possible interactions between verapamil and disopyramide phosphate are not available. Therefore, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Flecainide

A study of healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

Quinidine

In a small number of patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

The electrophysiological effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on AV conduction. There has been a report of increased quinidine levels during verapamil therapy.

Antihypertensive Agents

Concomitant use of TARKA with other antihypertensive agents including diuretics, vasodilators, beta-adrenergic blockers, and alpha-antagonists may result in additive hypotensive effects. There are reports that verapamil may result in higher concentrations of the alpha-agonists prazosin and terazosin.

Beta Blockers

Verapamil Component

Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction, and/or cardiac contractility. Drug interaction studies have indicated that the maximum concentrations of metoprolol and propranolol are increased after the administration of verapamil. The use of verapamil in combination with a beta-adrenergic blocker should be used only with caution, and close monitoring.

Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eyedrops and oral verapamil.

Concomitant Diuretic Therapy

Trandolapril Component

As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with TARKA. The possibility of exacerbation of hypotensive effects with TARKA may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with TARKA. If it is not possible to discontinue the diuretic, the starting dose of TARKA should be reduced (see **DOSAGE AND ADMINISTRATION**). No clinically significant pharmacokinetic interaction has been found between trandolapril (or its metabolites) and furosemide.

Agents Increasing Serum Potassium

Trandolapril Component

Trandolapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. Use of potassium-sparing diuretics (spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes concomitantly with ACE inhibitors can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be used with caution and with appropriate monitoring of serum potassium (see **PRECAUTIONS**).

HMG-CoA Reductase Inhibitors (“Statins”)

Verapamil component

The use of HMG-CoA reductase inhibitors that are CYP3A4 substrates in combination with verapamil has been associated with reports of myopathy/rhabdomyolysis.

Co-administration of multiple doses of 10 mg of verapamil with 80 mg simvastatin resulted in exposure to simvastatin 2.5-fold that following simvastatin alone. Limit the dose of simvastatin in patients on verapamil to 10 mg daily. Limit the daily dose of lovastatin to 40 mg. Lower starting and maintenance doses of other CYP3A4 substrates (e.g., atorvastatin) may be required as verapamil may increase the plasma concentration of these drugs.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

Trandolapril component

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including trandolapril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving trandolapril and NSAID therapy.

The antihypertensive effect of ACE inhibitors, including trandolapril may be attenuated by NSAIDs.

Other (Verapamil Component)

Nitrates

Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and the clinical experience suggest beneficial interactions.

Carbamazepine

Verapamil may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Anti-infective Agents

Therapy with rifampin may markedly reduce oral verapamil bioavailability. There have been reports that erythromycin and telithromycin may increase concentrations of verapamil.

Barbiturates

Phenobarbital therapy may increase verapamil clearance.

Immunosuppressive Agents

Verapamil therapy may increase serum levels of cyclosporin, sirolimus and tacrolimus.

Theophylline

Verapamil therapy may inhibit the clearance and increase the plasma levels of theophylline.

Tranquilizers/ Anti-depressants

Due to metabolism via the CYP enzyme system, there have been reports that verapamil may increase the concentrations of buspirone, midazolam, almotriptan and imipramine.

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-gp. Verapamil is known to inhibit CYP3A and P-gp. When verapamil and colchicine are administered together, the potential inhibition of P-gp and/or CYP3A by verapamil may lead to increased exposure to colchicine (see **PRECAUTIONS-Drug Interactions**).

Other

Concentrations of verapamil may be increased by the concomitant administration of protease inhibitors such as ritonavir, and reduced by the concomitant administration of sulfinpyrazone, or St John's Wort.

Concentrations of doxorubicin may be increased by the administration of verapamil.

There have been reports that verapamil may elevate the concentrations of the oral anti-diabetic glyburide.

Inhalation Anesthetics

Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil, should be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents

Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including TARKA.

Other (Trandolapril Component)

No clinically significant pharmacokinetic interaction has been found between trandolapril (or its metabolites) and nifedipine.

The anticoagulant effect of warfarin was not significantly changed by trandolapril.

Anti-diabetic Agents

The concomitant use of ACE inhibitors such as trandolapril with antidiabetic medications (insulin or oral hypoglycemic agents) may result in increased blood glucose lowering effects.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Verapamil Component

An 18-month toxicity study in rats, at a low multiple (6 fold) of the maximum recommended human dose, and not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for two years at doses of 10, 35, and 120 mg/kg per day or approximately 1x, 3.5x, and 12x, respectively, the maximum recommended human daily dose (480 mg per day or 9.6 mg/kg/day).

Verapamil was not mutagenic in the Ames test in 5 test strains at 3 mg per plate, with or without metabolic activation.

Studies in female rats at daily dietary doses up to 5.5 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

Long-term studies were conducted with oral trandolapril administered by gavage to mice (78 weeks) and rats (104 and 106 weeks). No evidence of carcinogenic potential was seen in mice dosed up to 25 mg/kg/day (85

mg/m²/day) or rats dosed up to 8 mg/kg/day (60 mg/m²/day). These doses are 313 and 32 times (mice), and 100 and 23 times (rats) the maximum recommended human daily dose (MRHDD) of 4 mg based on body-weight and body-surface-area, respectively assuming a 50 kg individual. The genotoxic potential of trandolapril was evaluated in the microbial mutagenicity (Ames) test, the point mutation and chromosome aberration assays in Chinese hamster V79 cells, and the micronucleus test in mice. There was no evidence of mutagenic or clastogenic potential in these *in vitro* and *in vivo* assays.

Reproduction studies in rats did not show any impairment of fertility at doses up to 100 mg/kg/day (710 mg/m²/day) of trandolapril, or 1250 and 260 times the MRHDD on the basis of body-weight and body-surface-area, respectively.

Pregnancy

Female patients of childbearing age should be told about the consequences of exposure to TARKA during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

Nursing Mothers

Verapamil is excreted in human milk. Radiolabeled trandolapril or its metabolites are secreted in rat milk. TARKA should not be administered to nursing mothers.

Geriatric Use

In placebo-controlled studies, where 23% of patients receiving TARKA were 65 years and older, and 2.4% were 75 years and older, no overall differences in effectiveness or safety were observed between these patients and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use

Neonates with a history of *in utero* exposure to TARKA:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

The safety and effectiveness of TARKA in children below the age of 18 have not been established.

Animal Pharmacology and/or Animal Toxicology

In chronic animal toxicology studies, verapamil caused lenticular and/or suture line changes at 30 mg/kg/day or greater and frank cataracts at 62.5 mg/kg/day or greater in the beagle dog but not the rat. Development of cataracts due to verapamil has not been reported in man.

ADVERSE REACTIONS

TARKA has been evaluated in over 1,957 subjects and patients. Of these, 541 patients, including 23% elderly patients, participated in U.S. controlled clinical trials, and 251 were studied in foreign controlled clinical trials. In clinical trials with TARKA, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with verapamil or trandolapril. TARKA has been evaluated for long-term safety in 272 patients treated for 1 year or more. Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events in U.S. placebo-controlled hypertension studies was required in 2.6% and 1.9% of patients treated with TARKA and placebo, respectively.

Adverse experiences occurring in 1% or more of the 541 patients in placebo-controlled hypertension trials who were treated with a range of trandolapril (0.5-8 mg) and verapamil (120-240 mg) combinations are shown below.

ADVERSE EVENTS OCCURRING in \geq 1% of TARKA PATIENTS IN U.S. PLACEBO-CONTROLLED TRIALS

	TARKA (N = 541) % Incidence (% Discontinuance)	PLACEBO (N = 206) % Incidence (% Discontinuance)
AV Block First Degree	3.9 (0.2)	0.5 (0.0)
Bradycardia	1.8 (0.0)	0.0 (0.0)
Bronchitis	1.5 (0.0)	0.5 (0.0)
Chest Pain	2.2 (0.0)	1.0 (0.0)
Constipation	3.3 (0.0)	1.0 (0.0)
Cough	4.6 (0.0)	2.4 (0.0)
Diarrhea	1.5 (0.2)	1.0 (0.0)
Dizziness	3.1 (0.0)	1.9 (0.5)
Dyspnea	1.3 (0.4)	0.0 (0.0)
Edema	1.3 (0.0)	2.4 (0.0)
Fatigue	2.8 (0.4)	2.4 (0.0)
Headache(s) ⁺	8.9 (0.0)	9.7 (0.5)
Increased Liver Enzymes*	2.8 (0.2)	1.0 (0.0)
Nausea	1.5 (0.2)	0.5 (0.0)
Pain Extremity(ies)	1.1 (0.2)	0.5 (0.0)
Pain Back ⁺	2.2 (0.0)	2.4 (0.0)
Pain Joint(s)	1.7 (0.0)	1.0 (0.0)
Upper Respiratory Tract Infection(s) ⁺	5.4 (0.0)	7.8 (0.0)
Upper Respiratory Tract Congestion ⁺	2.4 (0.0)	3.4 (0.0)

* Also includes increase in SGPT, SGOT, Alkaline Phosphatase

+ Incidence of adverse events is higher in Placebo group than TARKA patients

Other clinical adverse experiences possibly, probably, or definitely related to drug treatment occurring in 0.3% or more of patients treated with trandolapril/verapamil combinations with or without concomitant diuretic in controlled or uncontrolled trials (N = 990) and less frequent, clinically significant events (in italics) include the following:

Cardiovascular

Angina, AV block second degree, bundle branch block, edema, flushing, hypotension, myocardial infarction , palpitations, premature ventricular contractions, nonspecific ST-T changes, near syncope, tachycardia.

Central Nervous System

Drowsiness, hypesthesia, insomnia, loss of balance, paresthesia, vertigo.

Dermatologic

Pruritus, rash.

Emotional, Mental, Sexual States

Anxiety, impotence, abnormal mentation.

Eye, Ear, Nose, Throat

Epistaxis, tinnitus, upper respiratory tract infection, blurred vision.

Gastrointestinal

Diarrhea, dyspepsia, dry mouth, nausea.

General Body Function

Chest pain, malaise, weakness.

Genitourinary

Endometriosis, hematuria, nocturia, polyuria, proteinuria.

Hemopoietic

Decreased leukocytes, decreased neutrophils.

Musculoskeletal System

Arthralgias/myalgias, gout (increased uric acid).

Pulmonary

Dyspnea.

Angioedema

Angioedema has been reported in 3 (0.15%) patients receiving TARKA in U.S. and foreign studies (N = 1,957). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with TARKA should be discontinued and appropriate therapy instituted immediately (see **WARNINGS**).

Hypotension

(See **WARNINGS**.) In hypertensive patients, hypotension occurred in 0.6% and near syncope occurred in 0.1%. Hypotension or syncope was a cause for discontinuation of therapy in 0.4% of hypertensive patients.

Treatment of Acute Cardiovascular Adverse Reactions

The frequency of cardiovascular adverse reactions which require therapy is rare, hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occur following oral administration of TARKA (verapamil component), the appropriate emergency measures should be applied immediately, e.g., intravenously administered isoproterenol HCl, levarterenol bitartrate, atropine (all in the usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy (IHSS), alpha-adrenergic agents (phenylephrine, metaraminol bitartrate or methoxamine) should be used to maintain blood pressure, and isoproterenol and levarterenol should be avoided. If further support is necessary, inotropic agents (dopamine or dobutamine) may be administered. Actual treatment and dosage should depend on the severity and the clinical situation and the judgment and experience of the treating physician.

Other adverse experiences (in addition to those in table and listed above) that have been reported with the individual components are listed below.

Verapamil Component

Cardiovascular

(See **WARNINGS**.) CHF/pulmonary edema, AV block 3°, atrioventricular dissociation, claudication, purpura (vasculitis), syncope.

Digestive System

Gingival hyperplasia. Reversible, (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently reported in association with the use of verapamil.

Hemic and Lymphatic

Ecchymosis or bruising.

Nervous System

Cerebrovascular accident, confusion, psychotic symptoms, shakiness, somnolence.

Skin

Exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiform.

Urogenital

Gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation.

Trandolapril Component

Emotional, Mental, Sexual States

Decreased libido.

Gastrointestinal

Pancreatitis.

Clinical Laboratory Test Findings

Hematology

(See **WARNINGS**). Low white blood cells, low neutrophils, low lymphocytes, low platelets.

Serum Electrolytes

Hyperkalemia (see **PRECAUTIONS**), hyponatremia.

Renal Function Tests

Increases in creatinine and blood urea nitrogen levels occurred in 1.1 percent and 0.3 percent, respectively, of patients receiving TARKA with or without hydrochlorothiazide therapy. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see **PRECAUTIONS** and **WARNINGS**).

Liver Function Tests

Elevations of liver enzymes (SGOT, SGPT, LDH, and alkaline phosphatase) and/or serum bilirubin occurred. Discontinuation for elevated liver enzymes occurred in 0.9 percent of patients (see **WARNINGS**).

Post Marketing Experience

There has been a single postmarketing report of paralysis (tetraparesis) associated with the combined use of verapamil and colchicine. This may have been caused by colchicine crossing the blood-brain barrier due to CYP3A4 and P-gp inhibition by verapamil. Combined use of verapamil and colchicine is not recommended (see **PRECAUTIONS-Drug Interactions**).

OVERDOSAGE

No specific information is available on the treatment of overdose with TARKA.

Verapamil Component

Overdose with verapamil may lead to pronounced hypotension, bradycardia, and conduction system abnormalities (e.g., junctional rhythm with AV dissociation and high degree AV block, including asystole).

Other symptoms secondary to hypoperfusion (e.g., metabolic acidosis, hyperglycemia, hyperkalemia, renal dysfunction, and convulsions) may be evident.

Treat all verapamil overdoses as serious and maintain observation for at least 48 hours, preferably under continuous hospital care. Delayed pharmacodynamic consequences may occur with the sustained release formulation. Verapamil is known to decrease gastrointestinal transit time. In cases of overdose, tablets of ISOPTIN SR have occasionally been reported to form concretions within the stomach or intestines. These concretions have not been visible on plain radiographs of the abdomen, and no medical means of gastrointestinal emptying is of proven efficacy in removing them. Endoscopy might reasonably be considered in cases of overdose when symptoms are unusually prolonged. Verapamil cannot be removed by hemodialysis.

Treatment of overdosage should be supportive. Beta adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel, and have been used effectively in treatment of deliberate overdosage with verapamil. The following measures may be considered:

Bradycardia and Conduction System Abnormalities

Atropine, isoproterenol, and cardiac pacing.

Hypotension

Intravenous fluids, vasopressors (e.g., dopamine, dobutamine), calcium solutions (e.g., 10% calcium chloride solution).

Cardiac Failures

Inotropic agents (e.g., isoproterenol, dopamine, dobutamine), diuretics. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

Trandolapril Component

The oral LD₅₀ of trandolapril in mice was 4875 mg/kg in males and 3990 mg/kg in females. In rats, an oral dose of 5000 mg/kg caused low mortality (1 male out of 5; 0 females). In dogs, an oral dose of 1000 mg/kg did not cause mortality and abnormal clinical signs were not observed.

In humans, the most likely clinical manifestation would be symptoms attributable to severe hypotension. Laboratory determinations of serum levels of trandolapril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of trandolapril overdose. No data are available to suggest that physiological maneuvers (e.g., maneuvers to change pH of the urine) might accelerate elimination of trandolapril and its metabolites. It is not known if trandolapril or trandolaprilat can be usefully removed from the body by hemodialysis.

Angiotensin II could presumably serve as a specific antagonist antidote in the setting of trandolapril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive

effect of trandolapril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat trandolapril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

The recommended usual dosage range of trandolapril for hypertension is 1 to 4 mg per day administered in a single dose or two divided doses. The recommended usual dosage range of Isoptin-SR for hypertension is 120 to 480 mg per day administered in a single dose or two divided doses.

The hazards (see **WARNINGS**) of trandolapril are generally independent of dose; those of verapamil are a mixture of dose-dependent phenomena (primarily dizziness, AV block, constipation) and dose-independent phenomena, the former much more common than the latter. Therapy with any combination of trandolapril and verapamil will thus be associated with both sets of dose-independent hazards. The dose-dependent side effects of verapamil have not been shown to be decreased by the addition of trandolapril nor vice versa.

Rarely, the dose-independent hazards of trandolapril are serious. To minimize dose-independent hazards, it is usually appropriate to begin therapy with TARKA only after a patient has either (a) failed to achieve the desired antihypertensive effect with one or the other monotherapy at its respective maximally recommended dose and shortest dosing interval, or (b) the dose of one or the other monotherapy cannot be increased further because of dose-limiting side effects.

Clinical trials with TARKA have explored only once-a-day doses. The antihypertensive effect and or adverse effects of adding 4 mg of trandolapril once-a-day to a dose of 240 mg Isoptin-SR administered twice-a-day has not been studied, nor have the effects of adding as little of 180 mg Isoptin-SR to 2 mg trandolapril administered twice-a-day been evaluated. Over the dose range of Isoptin-SR 120 to 240 mg once-a-day and trandolapril 0.5 to 8 mg once-a-day, the effects of the combination increase with increasing doses of either component.

Replacement Therapy

For convenience, patients receiving trandolapril (up to 8 mg) and verapamil (up to 240 mg) in separate tablets, administered once-a-day, may instead wish to receive tablets of TARKA containing the same component doses.

TARKA should be administered with food.

HOW SUPPLIED

TARKA 2/180 mg tablets are supplied as pink, oval, film-coated tablets containing 2 mg trandolapril in an immediate release form and 180 mg verapamil hydrochloride in a sustained release form. The tablet is debossed with a triangle and 182 on one side and plain on the other side.

NDC 0074-3287-13 - bottles of 100

TARKA 1/240 mg tablets are supplied as white, oval, film-coated tablets containing 1 mg trandolapril in an immediate release form and 240 mg verapamil hydrochloride in a sustained release form. The tablet is debossed with a triangle and 241 on one side and plain on the other side.

NDC 0074-3288-13 - bottles of 100

TARKA 2/240 mg tablets are supplied as gold, oval, film-coated tablets containing 2 mg trandolapril in an immediate release form and 240 mg verapamil hydrochloride in a sustained release form. The tablet is debossed with a triangle and 242 on one side and plain on the other side.

NDC 0074-3289-13 - bottles of 100

TARKA 4/240 mg tablets are supplied as reddish-brown, oval, film-coated tablets containing 4 mg trandolapril in an immediate release form and 240 mg verapamil hydrochloride in a sustained release form. The tablet is debossed with a triangle and 244 on one side and plain on the other side.

NDC 0074-3290-13 - bottles of 100

Dispense in well-closed container with safety closure.

Storage

Store at 15°-25°C (59°-77°F) see USP.

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