PRODUCT MONOGRAPH

PrTARKA®

Sustained-Release Tablets

trandolapril/verapamil hydrochloride

1/180 mg, 2/180 mg, 1/240 mg, 2/240 mg, 4/240 mg

Antihypertensive Agent

Abbott Laboratories, Limited
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Date of Preparation:
June 22, 2001

Date of Revision:
February 13, 2007

Submission Control No.: 109661

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Film coated tablets / 1/180 mg 2/180 mg 1/240 mg 2/240 mg 4/240 mg	Corn starch, dioctyl sodium sulfosuccinate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, purified water, silicon dioxide, sodium alginate, sodium stearyl fumarate, synthetic iron oxides, talc, titanium dioxide

INDICATIONS AND CLINICAL USE

TARKA® (trandolapril/verapamil hydrochloride) is indicated for:

- treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.

Patients should be titrated with the individual drugs. If the fixed combination represents the dosage determined by this titration, the use of TARKA® may be more convenient in the management of patients. If during maintenance therapy dosage adjustment is necessary, it is advisable to use individual drugs.

Both trandolapril and verapamil SR should normally be used in those patients in whom treatment with a diuretic or a beta-blocker were found to be ineffective or were associated with unacceptable adverse effects. They can be tried as initial agents in those patients in whom diuretics and/or beta-blockers are contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

TARKA® is not indicated for initial therapy. Patients in whom trandolapril and verapamil SR are initiated simultaneously can develop symptomatic hypotension (see **WARNINGS AND PRECAUTIONS - Hypotension**).

In using trandolapril, consideration should be given to the risk of angioedema (see **WARNINGS AND PRECAUTIONS**).

Geriatrics (> 65 years of age):

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 on effectiveness or safety were observed between these patients and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatrics (< 18 years of age):

TARKA® has not been studied in children and therefore use in this age group is not recommended.

CONTRAINDICATIONS

- Patients who are hypersensitive to one of these two drugs or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Complicated myocardial infarction (patients who have ventricular failure manifested by pulmonary congestion).
- Severe left ventricular dysfunction (see **WARNINGS AND PRECAUTIONS - Heart Failure**).
- Hypotension (systolic pressure less than 90 mmHg) or cardiogenic shock.
- Second or third degree AV block (except in patients with a functioning artificial ventricular pacemaker).
- Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker).
- Marked bradycardia.
- Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes) (see **WARNINGS AND PRECAUTIONS - Accessory Bypass Tract**).
- A history of angioedema associated with prior angiotensin converting enzyme inhibitor (ACE) therapy.
- Pregnancy (see **WARNINGS AND PRECAUTIONS - Special Populations - Pregnant Women**).
- Nursing women (see **WARNINGS AND PRECAUTIONS - Special Populations - Nursing Women**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, ACE inhibitors can cause injury to or even death of the developing fetus. When pregnancy is detected or if the patient is planning to become pregnant, TARKA® should be discontinued as soon as possible (see **WARNINGS AND PRECAUTIONS - Pregnant Women**).

Cardiovascular

Hypotension

Concomitant therapy with ACE inhibitors and verapamil may result in hypotension. In controlled studies, hypotension was observed in 0.6% of uncomplicated hypertensive patients receiving TARKA® (trandolapril/verapamil hydrochloride) . Dizziness occurred more frequently than with placebo (see **ADVERSE REACTIONS**). In patients with angina or arrhythmias using antihypertensive drugs, the additional antihypertensive effect of TARKA® should be taken into consideration.

Hypotensive symptoms of lethargy and weakness with faintness have been reported following single oral doses of verapamil and even after some months of treatment. In some patients it may be necessary to reduce the dose.

Symptomatic hypotension has occurred after administration of trandolapril, usually after the first or second dose, or when the dose was increased. It is more likely to occur in patients who are volume depleted as a result of diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. Because of the potential fall in blood pressure in these patients, therapy with trandolapril should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of trandolapril is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response is not a contraindication to further doses which can be given usually without difficulty once the blood pressure has increased after volume expansion. If symptoms persist, the dosage should be reduced or the drug discontinued.

Heart Failure

Because of the drug's negative inotropic effect, verapamil should not be used in patients with poorly compensated congestive heart failure, unless the failure is complicated by or caused by a dysrhythmia. If verapamil is used in such patients, they must be digitalized prior to treatment.

It has been reported that digoxin plasma levels may increase with chronic verapamil administration (see **DRUG INTERACTIONS - Drug-Drug Interactions: Digoxin**) The use of verapamil in the treatment of hypertension is not recommended in patients with heart failure caused by systolic dysfunction.

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

Conduction Disturbance
Verapamil slows conduction across the A-V node and rarely may produce second or third degree A-V block, bradycardia and in extreme cases, asystole.

Because of the verapamil component, use TARKA® with caution in patients with first degree AV block.

Verapamil causes dose-related suppression of the S-A node. In some patients, sinus bradycardia may occur, especially in patients with a sick sinus syndrome (S-A nodal disease), which is more common in older patients (see **CONTRAINDICATIONS**).

Bradycardia
The total incidence of bradycardia with verapamil (ventricular rate less than 50 beats/min.) was 1.4% in controlled studies. Asystole in patients other than those with sick sinus syndrome is usually of short duration (few seconds or less), with spontaneous return to A-V nodal or normal sinus rhythm. If this does not occur promptly, appropriate treatment should be initiated immediately (see **OVERDOSAGE**).

Accessory Bypass Tract (Wolff-Parkinson-White or Lown-Ganong-Levine)
Verapamil may result in significant acceleration of ventricular response during atrial fibrillation or atrial flutter in the Wolff-Parkinson-White (WPW) or Lown-Ganong-Levine syndromes after receiving intravenous verapamil. 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**).

Concomitant Use With Beta-blockers
Generally, oral verapamil should not be given to patients receiving beta blockers since the depressant effects on myocardial contractility, heart rate and A-V conduction may be additive. However, in exceptional cases when in the opinion of the physician concomitant use in angina and arrhythmia is considered essential, such use should be instituted gradually under careful supervision. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out and the need for continued concomitant treatment periodically assessed.

Verapamil gives no protection against the dangers of abrupt beta-blocker withdrawal and such

withdrawal should be done by the gradual reduction of the dose of beta blocker. Then verapamil may be started with the usual dose.

Patients with Hypertrophic Cardiomyopathy
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, but in some cases verapamil use had to be discontinued.

Aortic Stenosis
TARKA® should not be used in patients with aortic stenosis.

Immune

Angioedema
Angioedema has been reported in patients taking ACE inhibitors, including trandolapril. Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, trandolapril should be discontinued immediately, the patient treated appropriately 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. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see **ADVERSE REACTIONS**).

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see **CONTRAINDICATIONS**).

The incidence of angioedema during ACE inhibition therapy has been reported to be higher in black than in non-black patients.

Hematologic

Neutropenia/Agranulocytosis
Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Current experience with trandolapril shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease.

Hepatic/Biliary/Pancreatic

Hepatic Failure / Elevated Liver Enzymes
Elevations of transaminases, with and without concomitant elevations in alkaline phosphatase and bilirubin, have been reported. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge. Clinical symptoms of malaise, fever, and/or right upper quadrant pain, in addition to elevations of SGOT, SGPT, and alkaline phosphatase have been reported. Periodic monitoring of liver function in patients receiving TARKA® is, therefore, prudent.

In rare instances, ACE inhibitors have been associated with a syndrome of cholestatic jaundice, fulminant hepatic necrosis and death. The mechanism of this syndrome is not understood.

Patients receiving TARKA® who develop jaundice should discontinue therapy and receive appropriate medical follow-up.

Liver abnormalities (increased SGOT, increased SGPT, increased liver enzyme and liver function abnormal) associated to TARKA were noted in only 1.2% of patients during TARKA clinical studies.

Use in Patients with Hepatic Impairment
In patients with impaired liver function, the elimination $t_{½}$ of verapamil is prolonged four-fold and the plasma concentrations of trandolapril and, to a lesser extent, of its principle active metabolite, trandolaprilat, are increased (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**). Accordingly, a decreased dosage of TARKA® should be used in these patients (see **DOSAGE AND ADMINISTRATION**).

In these patients, careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects should be carried out during TARKA® therapy.

Renal

Use in Patients with Renal Impairment
About 70% of an administered dose of verapamil is excreted as metabolites in the urine. In one study in healthy volunteers, the total body clearance after intravenous administration of verapamil was 12.08 mL/min/kg, while in patients with advanced renal disease it was reduced to 5.33 mL/min/kg. This pharmacokinetic finding suggests that renal clearance of verapamil in patients with renal disease is decreased. In two studies with oral verapamil no difference in pharmacokinetics could be demonstrated. Therefore, until further data are available, verapamil should be used with caution in patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effect (see **DOSAGE AND ADMINISTRATION**).

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive

azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

Use of trandolapril should include appropriate assessment of renal function.

Anaphylactoid reactions during membrane exposure
Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Ear/Nose/Throat

As with other ACE inhibitors, dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of trandolapril, has been reported. Such possibility should be considered as part of the differential diagnosis of cough.

Special Populations

Pregnant Women

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected or if the patient is planning to become pregnant, TARKA® should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

Prematurity, and patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have also been reported following ACE inhibitor exposure in the first trimester of pregnancy.

Infants with a history of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/ or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

Verapamil hydrochloride cannot be removed by hemodialysis. It is not known if trandolapril or trandolaprilat can be removed from the body by hemodialysis.

Nursing Women

The presence of concentrations of ACE inhibitor have been reported in human milk. Use of ACE inhibitors is not recommended during breast-feeding. If breast-feeding needs to be continued, alternative measures to control the patient's blood pressure need to be put in place.

TARKA® is not recommended in these patients because of the potential for adverse reactions in nursing infants. The verapamil component of TARKA® is secreted in human milk. Following administration of radio-labelled trandolapril to lactating rats, radioactivity has been detected in the milk.

Breast feeding should be discontinued during TARKA® therapy.

Labour and Delivery - It is not known whether the use of verapamil during labour or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labour or increases the need for forceps delivery or other obstetric intervention.

Pediatrics (< 18 years of age)
The safety and effectiveness of TARKA® in children below the age of 18 have not been established. Therefore, use in this group is not recommended.

Geriatrics (> 65 years of age)
Although clinical experience has not identified differences in response between the elderly (≥ 65 years) and younger patients (<65 years), greater sensitivity of some older individuals to TARKA® cannot be ruled out (see **ACTION AND CLINICAL PHARMACOLOGY** - **Pharmacokinetics**).

Caution should be exercised when verapamil is administered to elderly patients (≥ 65 years) especially those prone to developing hypotension or those with a history of cerebrovascular insufficiency (see **DOSAGE AND ADMINISTRATION**). The adverse reactions occurring more frequently include dizziness and constipation. Serious adverse events associated with heart block have occurred in the elderly.

Carcinogenesis and Mutagenesis

There was no evidence of a carcinogenic effect when verapamil hydrochloride was administered orally (diet) to male and female rats at doses up to 112.2 and 102.5 mg/kg/day, respectively, for 24 months, or when trandolapril was administered by gavage for 18 months to mice at doses up to 25 mg/kg/day and to rats at doses up to 8 mg/kg/day.

The mutagenic potential trandolapril/verapamil hydrochloride (1:60) was evaluated in four assays: the Salmonella/microsome (AMES) assay, the HPRT test on the V79 cell line, an *in vitro* chromosomal aberration test, and the chromosomal aberration test in the bone marrow of the Chinese hamster. The results obtained from these studies indicated that there were no gene

mutations induced by the combination in any of the five salmonella typhimurium mutants or at the HPRT locus in V79 cells, and that the induction of structural chromosome aberrations and numerical aberrations by trandolapril and verapamil hydrochloride could be ruled out. (See **TOXICOLOGY - Long-term Toxicity: Carcinogenicity, Mutagenicity**).

ADVERSE REACTIONS

Overview

The combination of trandolapril and verapamil SR has been evaluated in over 1,957 subjects and patients. Of these, 541 patients (including 23% elderly patients) participated in North American placebo-controlled clinical trials, and 251 were studied in European placebo-controlled clinical trials. This combination has been evaluated for long-term safety in 272 patients treated for 1 year or more.

The most frequent adverse events in controlled clinical trials conducted in North America with trandolapril and verapamil SR were (n=541): first degree AV block (3.9%); cough (4.6%); constipation (3.3%) and dizziness (3.1%).

The most serious adverse reactions with TARKA (trandolapril/verapamil hydrochloride) are second degree AV block, angina, hypotension and angioedema.

Discontinuation of therapy because of adverse events in North American placebo-controlled hypertension studies was required in 2.6% and 1.9% of patients treated with (trandolapril/verapamil hydrochloride) and placebo, respectively.

Hypotension - In hypertensive patients in controlled and uncontrolled trials, hypotension occurred in 0.6% and near syncope occurred in 0.1% (possibly, probably or definitely related to combination treatment). Hypotension or syncope was a cause for discontinuation of therapy in 0.4% of hypertensive patients in North American controlled studies (see **WARNINGS AND PRECAUTIONS - Hypotension**).

Adverse experiences occurring more commonly with combination therapy than placebo in 1% or more of the 541 patients in North American placebo-controlled hypertension trials are shown in the following table.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Most Common Drug Adverse Reactions (≥1%)

Adverse experiences occurring more commonly with combination therapy than placebo in 1% or more of the 541 patients in North American placebo-controlled hypertension trials are shown in Table 1.

Table 1
Adverse Drug Reactions in North American 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)
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 Joint(s)	1.7 (0.0)	1.0 (0.0)

* Also includes increase in SGPT, SGOT, Alkaline Phosphatase

Less Common Clinical Trial Adverse Drug Reactions (≤1%)

Other clinical adverse experiences possibly, probably, or definitely related to drug treatment, occurring in 0.3% or more of patients treated with (trandolapril/verapamil hydrochloride) in controlled, or uncontrolled trials (N=990) and less frequent, clinically significant events (in italics) include the following:

Cardiovascular:	angina, second degree AV block, bundle branch block, edema, flushing, hypotension, myocardial infarction, palpitations, premature ventricular contractions, nonspecific ST-T changes, near syncope, tachycardia.
Central Nervous Systems:	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:	dyspepsia, dry mouth, nausea.
General Body Function:	chest pain, malaise, weakness.
Genitourinary:	endometriosis, hematuria, nocturia, polyuria, proteinuria.
Hemopoietic:	decreased leukocytes, decreased neutrophils.

Metabolism and Endocrine Function: increased alkaline phosphatase, increased liver enzymes, increased potassium, increased SGOT.

Musculoskeletal System:	arthralgia, myalgia, gout, increased uric acid.
Pulmonary:	dyspnea.
Angioedema:	Angioedema and/or facial edema has been reported in 3 (0.15%) patients receiving (trandolapril/verapamil hydrochloride) in North American and European 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 (trandolapril/verapamil hydrochloride) should be discontinued and appropriate therapy instituted immediately (see **WARNINGS AND PRECAUTIONS** - **Angioedema**).

In addition to those reported above, other adverse experiences have previously been reported with the individual components, verapamil hydrochloride and trandolapril:

Verapamil Component Adverse Reactions

Cardiovascular:	CAF/pulmonary edema, third degree AV block, atrioventricular dissociation, claudication, syncope (see **WARNINGS AND PRECAUTIONS** - **Hypotension**).
Digestive System:	nausea, gingival hyperplasia, reversible paralytic ileus.
Hemic and Lymphatic:	ecchymosis or bruising.
Nervous System:	cerebrovascular accident, confusion, psychotic symptoms, shakiness, somnolence.
Skin:	exanthema, hair loss, hyperkeratosis, purpura (vasculitis), sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme.
Urogenital:	gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation.

Trandolapril Component Adverse Reactions

Body as a whole:	asthenia, abnormal feeling, abdominal pain, pain in extremities.
Cardiovascular:	hypertension, migraine, syncope.
Dermatology:	urticaria, pemphigus, Stevens-Johnson Syndrome.
Gastrointestinal:	gastrointestinal pain, gastrointestinal disorder, anorexia, abnormal liver function test, vomiting, pancreatitis.
Nervous system:	depression, sleep disorder, decreased libido, hot flushes.
Respiratory system:	bronchitis, pharyngitis.
Other:	cramps, increased urinary frequency, edema, taste disorders, anaphylactoid reaction.

A symptom complex has been reported which may include fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leucocytosis. Rash, photosensitivity or other dermatologic manifestations may also occur.

Clinical Laboratory Testing Findings

Hematology:	leucopenia, neutropenia, lymphopenia, thrombocytopenia (see **WARNINGS AND PRECAUTIONS** - **Neutropenia/ Agranulocytosis**).
Serum Electrolytes:	Hyperkalemia (see **WARNINGS AND PRECAUTIONS** - **Hyperkalemia and Potassium - Sparing Diuretics), 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 (trandolapril/verapamil hydrochloride) 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 **WARNINGS AND PRECAUTIONS** - **Use in Patients with Renal Impairment**).
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 AND PRECAUTIONS** - **Elevated Liver Enzymes/Hepatic Failure**).

DRUG INTERACTIONS

Overview

As with all drugs, care should be exercised when treating patients with multiple medications. Verapamil undergoes biotransformation by the CYP3A4, CYP1A2, CYP2C9 isoenzymes of the cytochrome P450 system. Verapamil has been shown to be an inhibitor of CYP3A4 enzymes. Coadministration of verapamil with other drugs which follow the same route of biotransformation or are inhibitors or inducers of these enzymes may result in altered bioavailability of verapamil or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered verapamil to maintain optimum therapeutic blood levels.

Drug-Drug Interactions

Vasodilators: Concomitant use with vasodilators may cause a potentiation of the hypotensive effect.

Interactions due to Verapamil Hydrochloride Component

Table 2 summarizes potential drug interactions with TARKA due to the verapamil hydrochloride component.

Table 2
Potential Drug Interactions Associated with Verapamil

Concomitant Drug Class: Drug Name	Effect on Concentration of Verapamil or Concomitant Drug	Clinical Comment
Alpha blockers: Prazosin, Terazosin	↑ prazosin C_{max} (~40%) with no effect on $t_{½}$	
	↑ terazosin AUC (~24%) and C_{max} (~25%)	Clinically significant transient orthostatic hypotension may occur upon initiation of combined therapy.
Antiarrhythmics: Flecainide, Quinidine	Minimal effect on flecainide plasma clearance (<~10%); no effect on verapamil plasma clearance.	The concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarisation. May also have negative inotropic effect and prolongation of atrioventricular conduction.
	↓ oral quinidine clearance (~35%)	In a small number of patients with hypertrophic cardiomyopathy, concomitant use of verapamil and quinidine resulted in significant hypotension and may result in pulmonary edema. Until further data are obtained, combined therapy of TARKA® and quinidine in patients with hypertrophic cardiomyopathy should 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.
Antiasthmatics: Theophylline	↓ oral and systemic clearance of theophylline by ~20%. Reduction of clearance was lessened in smokers.	Caution should be exercised when co-administering theophylline and TARKA®.
Anticonvulsants: Carbamazepine	↑ carbamazepine AUC (~46%) in refractory partial epilepsy patients	Concomitant oral use may potentiate the effects of carbamazepine neurotoxicity. Symptoms include nausea, diplopia, headache, ataxia or dizziness.

Concomitant Drug Class: Drug Name	**Effect on Concentration of Verapamil or Concomitant Drug**	**Clinical Comment**
Antidepressants: Imipramine	↑ imipramine AUC (~15%). No effect on level of active metabolite desipramine	As with all antihypertensive agents, there is an elevated risk of orthostatic hypotension when combining TARKA® with major tranquilizers or tricyclic antidepressants, such as imipramine.
Antidiabetics: Glibenclamide	↑ glibenclamide C_{max} (~28%), AUC (~26%)	
Anti-infectives: Rifampin, Erythromycin, Telithromycin	Rifampin: ↓ verapamil AUC (~97%), C_{max} (~ 94%) oral bioavailability (~92%) Possible ↑ in verapamil when used in combination with either erythromycin or telithromycin	Blood pressure lowering effect of verapamil may be reduced when used concomitantly with rifampin.
Antineoplastics: Doxorubicin	↑ doxorubicin AUC (89%) and C_{max} (61%) with oral verapamil administration in patients with small cell lung cancer. In patients with advanced neoplasm, intravenous verapamil did not change significantly doxorubicin PK.	Verapamil inhibits P-glycoprotein mediated transport of anti-neoplastic agents out of tumour cells, resulting in their decreased metabolic clearance. Dosage adjustments of anti-neoplastic agents should be considered when verapamil is administered concomitantly.
Barbiturates: Phenobarbital	↑ oral verapamil clearance (~5-fold)	
Benzodiazepines and other anxiolytics: Buspirone, Midazolam	↑ buspirone AUC, C_{max} by ~3.4-fold ↑ midazolam AUC (~3-fold) and, C_{max} (~2-fold)	
Beta blockers: Atenolol Metoprolol, Propranolol, Timolol	A variable increase in atenolol plasma concentration at steady state has been reported in patients with angina pectoris. ↑ metoprolol AUC (~32.5%) and Cmax (~41%) in patients with angina pectoris ↑ propanolol AUC (~65%), C_{max} (~ 94%) in patients with angina pectoris	Concomitant therapy may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility. (See **WARNINGS AND PRECAUTIONS**) Asymptomatic bradycardia (<36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eye drops and oral verapamil.

Concomitant Drug Class: Drug Name	**Effect on Concentration of Verapamil or Concomitant Drug**	**Clinical Comment**
Cardiac glycosides: Digitoxin, Digoxin	↓ digitoxin total body CL (~27%) and extrarenal clearance (~29%) ↑ digoxin levels ~50-75% during the first week of therapy ↑ digoxin AUC (~32%), C_{max} (~98%) in hepatic cirrhosis patients Healthy subjects: ↑ digoxin C_{max} by ~45% to 53% ↑ digoxin C_{ss} by ~42% and ↑ AUC by ~52%	The increase in digoxin levels can result in digoxin toxicity. 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 TARKA®, the patient should be reassessed to avoid underdigitalization. (See **WARNINGS AND PRECAUTIONS**)
H2 Receptor Antagonists: Cimetidine	In healthy subjects, ↑ AUC of R-(~25%) and S-(~40%) verapamil with corresponding ↓ in R- and S-verapamil clearance	
HIV antiviral agents		Due to the metabolic inhibitory potential of some of the HIV antiviral agents, such as ritonavir, plasma concentrations of verapamil may increase. Caution should be used or the dose of verapamil may be decreased.
Immunologics: Cyclosporine, Sirolimus, Tacrolimus	↑ cyclosporine AUC, C_{ss}, C_{max} by ~45% in renal transplant patients Possible ↑ sirolimus levels Possible ↑ tacrolimus levels	
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 hemodynamic effects.

Concomitant Drug Class: Drug Name	Effect on Concentration of Verapamil or Concomitant Drug	Clinical Comment
Lipid metabolism regulators: Atorvastatin, Lovastatin, Simvastatin	Possible ↑ atorvastatin levels Possible ↑ lovastatin levels ↑ simvastatin AUC (~4.6-fold), C_{max} (~2.6-fold) in healthy subjects	Treatment with HMG CoA reductase inhibitors (e.g., simvastatin/lovastatin) in a patient taking verapamil should be started at the lowest possible dose and titrated upwards. If verapamil treatment is to be added to patients already taking and HMG CoA reductase inhibitor (e.g., simvastatin/ lovastatin), consider a reduction in the statin dose and retitrate against serum cholesterol concentrations. There is no direct *in vivo* clinical evidence for an interaction between atorvastatin and verapamil, however, there is strong potential for verapamil to significantly affect atorvastatin pharmacokinetics in a similar manner to simvastatin and lovastatin. Consider using caution when atorvastatin and verapamil are concomitantly administered. Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and are less likely to interact with verapamil.
Lithium		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. Lithium based drugs should be administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be further increased.
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, therefore, be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.
Non-steroidal anti-inflammatory agents: Acetylsalicylic acid		Potential adverse reactions in terms of bleeding due to synergistic antiplatelet effects of acetylsalicylic acid and verapamil should be taken into consideration in patients taking the two agents concomitantly.
Serotonin receptor agonists: Almotriptan	↑ almotriptan AUC (~20%) ↑ C_{max} (~24%)	
Uricosurics: Sulfinylpyrazone	↑ verapamil oral clearance (~3-fold). ↓ bioavailability (~60%)	The blood pressure lowering effect of verapamil may be reduced.

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

Use in Patients with Attenuated (Decreased) Neuromuscular Transmission: 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. Accordingly, it may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission. (See **DRUG INTERACTIONS - Use in Surgery/Anaesthesia)**.

Interactions due to Trandolapril Component

Table 3 summarizes potential drug interactions with TARKA due to the trandolapril component.

Table 3
Potential Drug Interactions Associated with Trandolapril and Trandolaprilat

Concomitant Drug Class: Drug Name	**Effect on Concentration of trandolapril/trandolaprilat or concomitant drug**	**Clinical Comment**
Antacids	Antacids decrease the bioavailability of ACE inhibitors.	It is recommended to ingest these products separately.
Anticoagulants: Warfarin		In a multi-dose placebo-controlled pharmacodynamic study in healthy volunteers, the anticoagulant effect of warfarin was not significantly changed by trandolapril.
Beta Blockers: Propanolol	No effect on C_{max} and AUC of trandolaprilat. Trandolapril did not affect C_{max} and AUC of propranolol.	
Cardiac glycosides: Digoxin	In one open-label study conducted in eight healthy male volunteers, in which multiple therapeutic doses of both trandolapril and digoxin were administered, no changes were found in serum levels of trandolapril, trandolaprilat and digoxin.	Pharmacodynamically, the combination had a synergistic effect on left ventricular functions, as evidenced by the improvement in systolic time-intervals.

Concomitant Drug Class: Drug Name	Effect on Concentration of trandolapril/trandolaprilat or concomitant drug	Clinical Comment
Diuretics: Furosemide	No effect on C_{max} and AUC of trandolapril and trandolaprilat	Patients concomitantly taking antihypertensive therapy with diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of non-diuretic therapy. If it is not possible to discontinue the diuretic, the initial dose of antihypertensive therapy should be reduced and the patient observed closely for several hours following initiation of therapy (see **WARNINGS AND PRECAUTIONS - Hypotension**, and **DOSAGE AND ADMINISTRATION**).
Non-steroidal anti-inflammatory agents		The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of non-steroidal anti-inflammatory agents. The combination of trandolapril with non-steroidal anti-inflammatory agents predisposes to a risk of hyperkalemia particularly in cases of renal failure. Blood pressure and cardiac functions monitoring should be increased when any non-steroidal anti-inflammatory agent is added or discontinued in a patient treated with trandolapril.
H2 Receptor Antagonists: Cimetidine	No effect of cimetidine on C_{max} and AUC of trandolapril and trandolaprilat	
Lithium	Increased serum lithium levels have been reported in patients receiving concurrently ACE inhibitors and lithium.	Symptoms of lithium toxicity have been reported in patients receiving concurrently ACE inhibitors and lithium.

Agents Causing Renin Release: The antihypertensive effect of trandolapril is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

Agents Increasing Serum Potassium: Since trandolapril decreases aldosterone production, elevation of serum potassium may occur. Potassium sparing diuretics such as spironolactone, triamterene or amiloride, or potassium supplements should be given only for documented hypokalemia and with caution and frequent monitoring of serum potassium, since a significant increase in serum potassium could occur.

Salt substitutes which contain potassium should be used with caution.

Allopurinol, cytostatic, immunosuppressive agents, systemic corticosteroids or procainamide: Concomitant administration with ACE-inhibitors may lead to an increased risk of leucopenia.

Anaphylactoid reactions during LDL Apheresis: Rarely, patients receiving ACE inhibitors

during low density lipoprotein apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactoid reactions during desensitization: There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Use in Surgery/Anaesthesia: In patients undergoing major surgery or during anaesthesia 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 **DRUG INTERACTIONS - Use in Patients with Attenuated (Decreased) Neuromuscular Transmission**).

Hyperkalemia and Potassium - Sparing Diuretics: In clinical trials, hyperkalemia (serum potassium > 6.00 mEq/L) occurred in approximately 0.4 % of hypertensive patients receiving trandolapril and in 0.8% of patients receiving trandolapril concurrently with verapamil SR. 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 (see **DRUG INTERACTIONS - Agents Increasing Serum Potassium**).

Drug-Food Interactions

Administration of TARKA® with a high-fat meal does not alter the bioavailability of trandolapril, whereas verapamil peak concentrations and area under the curve (AUC) decrease 42% and 27%, respectively, relative to administration in the fasting state. Norverapamil values are also decreased 22% and 17%, respectively, in the fed state. Food thus decreases verapamil bioavailability, and results in a narrower peak to trough ratio.

In healthy volunteers, multiple high doses of grapefruit juice increased the AUC for S-verapamil and R-verapamil by up to 49% and 37%, respectively. The increase in C_{max} for S-verapamil and R-verapamil were up to 75% and 51%, respectively. Elimination half-life and renal clearance of both S- and R-verapamil were not affected.

Drug-Herb Interactions

In healthy volunteers, multiple doses of St John's wort decreased the AUC for R- and S- verapamil by 78% and 80%, respectively, with similar decreases in C_{max}.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been evaluated.

Drug-Lifestyle Interactions

Verapamil may increase blood alcohol concentrations and prolong its effects. Alcohol enhances the bioavailability of ACE inhibitors.

Depending on individual susceptibility, the patients' ability to drive a vehicle or operate machinery may be impaired, especially in the initial stages of treatment. TARKA® may increase the blood levels of alcohol and slow its elimination. The effects of alcohol may therefore be exaggerated.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosage must be individualized. The fixed combination is not for initial therapy. The dose of TARKA® (trandolapril/verapamil hydrochloride) should be determined by titration of the individual components.

Once the patient has been successfully titrated with the individual components as described below, TARKA® can be substituted if the titrated doses and dosing schedule can be achieved by the fixed combination (see **INDICATIONS AND CLINICAL USE,** and **WARNINGS AND PRECAUTIONS - Hypotension**). TARKA® is available at doses of 1/180 mg, 2/180 mg, 1/240 mg, 2/240 mg and 4/240 mg of trandolapril and verapamil SR, respectively.

For Verapamil Monotherapy
The dosage should be individualized by titration depending on patient tolerance and responsiveness to verapamil. Titration should be based on therapeutic efficacy and safety, evaluated weekly and approximately 24 hours after the previous dose.

The antihypertensive effects of verapamil SR are evident within the first week of therapy. Optimal doses are usually lower in patients also receiving diuretics since additive antihypertensive effects can be expected.

Patients with Hepatic and Renal Impairment - Verapamil SR should be administered cautiously to patients with liver or renal function impairment. The dosage should be carefully and gradually adjusted depending on patient tolerance and response. These patients should be monitored carefully for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil SR should not be used in severe hepatic dysfunction (see **WARNINGS AND PRECAUTIONS - Use in Patients with Hepatic Impairment**).

Switching from Verapamil Tablets to Verapamil SR - When switching from verapamil tablets to

verapamil SR, the total daily dose in milligrams may remain the same.

For Trandolapril Monotherapy
In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. If blood pressure is not controlled alone, a diuretic may be added.

Diuretic-treated Patients - Symptomatic hypotension occasionally may occur following the initial dose of trandolapril and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with trandolapril to reduce the likelihood of hypotension. If the diuretic cannot be discontinued, an initial dose of 0.5 mg trandolapril should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of trandolapril should subsequently be titrated to the optimal response.

Recommended Dose and Dosage Adjustment

For Verapamil Monotherapy

Adult: The usual initial adult dose is 180 to 240 mg/day. If required, the dose may be increased up to 240 mg twice a day. A maximum daily dose of 480 mg should not be exceeded.

Recommended dosing intervals for specific daily dosages are given below in table 4:

Table 4
Recommended Dosing Intervals for Specific Daily Dosages

TOTAL DAILY VERAPAMIL SR DOSE	RECOMMENDED DOSING INTERVALS
180 mg	Once each morning with food
240 mg	Once each morning with food
360 mg	180 mg each morning plus 180 mg each evening, with food; or 240 mg each morning plus 120 mg each evening, with food.
480 mg	240 mg each morning plus 240 mg each evening with food,

Elderly: Lower dosages of verapamil SR, i.e. 120 mg a day, may be warranted in elderly patients (i.e., 65 years and older). The dosage should be carefully and gradually adjusted depending on patient tolerability and response.

For Trandolapril Monotherapy

Adult: The recommended initial dosage for trandolapril is 1 mg once daily. Dosage should be adjusted according to blood pressure response at intervals of 2 to 4 weeks up to a maximum of 4 mg once daily. The usual maintenance dose is 1 to 2 mg once daily.

Elderly: In elderly patients with normal renal and hepatic function, no dosage adjustment is necessary.

However, as some elderly patients may be particularly susceptible to ACE inhibitors, administration of low initial doses and evaluation of the blood pressure response and of the renal function at the beginning of the treatment is recommended.

Dosage in Renal Impairment: For patients with a creatinine clearance below 30 mL/min/ 1.73 m^2, the recommended initial dose is 0.5 mg trandolapril once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 1 mg.

In patients with severe renal impairment (creatinine clearance below 10 mL/min/1.73 m^2) a daily

dosage of 0.5 mg in a single dose should not be exceeded.

Use in Hepatic Impairment: The recommended initial dose is 0.5 mg trandolapril once daily.

Administration

TARKA® tablets should not be divided, crushed or chewed. TARKA® should be taken with food (see **DRUG INTERACTIONS - Drug-Food Interactions**).

OVERDOSAGE

During overdose with TARKA® (trandolapril/verapamil hydrochloride), fatalities have occurred.

Verapamil Overdosage
Based on reports of intentional overdosage of verapamil hydrochloride, the following symptoms have been observed. Hypotension occurs, varying from transient to severe. Conduction disturbances seen included: prolongation of A-V conduction time, A-V dissociation, nodal rhythm, ventricular fibrillation and ventricular asystole.

Treatment of overdosage should be supportive. Gastric lavage should be undertaken, even later than 12 hours after ingestion, if no gastrointestinal motility is present. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion influx across the slow channel.

These pharmacologic interventions have been effectively used in treatment of overdosage with verapamil. Clinically significant hypotensive reactions should be treated with vasopressor agents. A-V block is treated with atropine and cardiac pacing. Asystole should be handled by the usual Advanced Cardiac Life Support measures including the use of vasopressor agents, e.g. isoproterenol hydrochloride. Verapamil is not removed by hemodialysis.

In case of overdosage with large amounts of verapamil SR it should be noted that the release of the active drug and the absorption in the intestine may take more than 48 hours. Depending on the time of ingestion, incompletely dissolved tablets may be present along the entire length of the gastrointestinal tract which function as active drug depots. Extensive elimination measures are indicated, such as induced vomiting, removal of the contents of the stomach and the small intestine under endoscopy, intestinal lavage and high enemas.

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment of the treating physician. Patients with hypertrophic cardiomyopathy treated with verapamil should not be administered positive inotropic agents. (Marked by asterisks, in the table 5, following):

Table 5 Overdosage Adverse Reactions and Recommended Treatments			
Adverse Reaction	**Proven Effective Treatment**	**Treatment with Good Theoretical Rationale**	**Supportive Treatment**
Shock, cardiac failure, severe Hypotension	Calcium salt e.g. calcium gluconate i.v.; i.v. metaraminol bitartrate*	i.v. dopamine HCl* i.v. dobutamine HCl*	i.v. fluids; Trendelenburg position
Bradycardia, A-V block, asystole	i.v. isoproterenol HCl*; i.v. atropine sulphate; Cardiac pacing		i.v. fluids (slow drip)
Rapid ventricular rate (due to antegrade conduction in flutter/fibrillation with W-P-W or L-G-L syndrome)	D.C. cardioversion (high energy may be required); i.v. procainamide; i.v. lidocaine HCl		i.v. fluids (slow drip)

Trandolapril Overdosage

The most likely clinical manifestations of overdosage of trandolapril would be symptoms attributable to severe hypotension, which should normally be treated by intravenous volume expansion with normal saline. It is not known if trandolapril or trandolaprilat can be removed from the body by hemodialysis.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TARKA® (trandolapril/verapamil hydrochloride) is a formulation containing slow-release verapamil, a phenylalkylamine calcium channel blocker, along with immediate-release trandolapril, an angiotensin converting enzyme (ACE) inhibitor.

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 reflex tachycardia. During isometric or dynamic exercise, verapamil does not blunt hemodynamic response in patients with normal ventricular function. Verapamil does not alter total serum calcium levels.

Trandolapril is a pro-drug. Trandolaprilat, its major active metabolite, inhibits ACE in human subjects and in animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the more pharmacologically active substance, angiotensin II. Angiotensin II has vasoconstrictor activity and also stimulates aldosterone secretion by the adrenal cortex.

Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

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

Pharmacodynamics

Controlled clinical studies have shown that the effects of concurrent use of verapamil SR and trandolapril are additive with respect to lowering systolic and diastolic blood pressure.

The antihypertensive effect of angiotensin converting enzyme inhibitors is generally lower in black patients than in non-blacks.

Pharmacokinetics

Absorption:

Following a single oral dose of TARKA® in healthy subjects, peak plasma concentrations are reached within 0.5 to 2 hours for trandolapril and within 4 to 15 hours for verapamil. Peak plasma concentrations of the active desmethyl metabolite of verapamil, norverapamil, are reached within 5 to 15 hours. Trandolapril disappears very rapidly from plasma and its $t_{1/2}$ is less than one hour. Cleavage of the ester group by hydrolysis converts trandolapril to its active diacid metabolite, trandolaprilat, which reaches peak plasma concentrations within 2 to 12 hours.

Trandolaprilat has an effective elimination t½ of approximately 10 hours while that of verapamil, as verapamil SR, is 6 to 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 twofold higher than those observed after a single oral dose of TARKA®.

Verapamil SR is a racemic mixture consisting of equal portions of the R enantiomer and the S enantiomer. More than 90% of the orally administered dose of verapamil SR is absorbed. Upon oral administration, there is rapid stereo selective biotransformation during the first pass of verapamil through the portal circulation. The S enantiomer is pharmacologically more active than the R enantiomer. There is a nonlinear correlation between the verapamil dose administered and verapamil plasma levels.

Metabolism: In healthy men, orally administered verapamil undergoes extensive metabolism by the cytochrome P-450 system. The particular isoenzymes involved are CYP3A4, CYP1A2, and CYP2C family. Thirteen metabolites have been identified in urine. Norverapamil can reach steady-state plasma concentrations approximately equal to those of verapamil itself. The cardiovascular activity of norverapamil appears to be approximately 20% that of verapamil. R-verapamil is 94% bound to plasma albumin, while S-verapamil is 88% bound. In addition, R-verapamil is 92% and S-verapamil 86% bound to alpha-1 acid glycoprotein. The degree of biotransformation during the first pass of verapamil may vary according to the status of the liver in different patient populations. In patients with hepatic insufficiency, metabolism is delayed and elimination t½ prolonged up to 14 to 16 hours (see **WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic**, and **DOSAGE AND ADMINISTRATION**).

Approximately 40 to 60% of an administered oral dose of trandolapril is absorbed. Trandolapril undergoes extensive first-pass metabolism in the liver, and this is the reason that its bioavailability is low: 7.5% (ranging from 4% to 14%). Minor metabolic pathways lead to the formation of diketopiperazine derivatives of trandolapril and trandolaprilat. These molecules have no ACE inhibitory activity. Glucuronide conjugated derivatives of trandolapril and trandolaprilat are also produced.

Distribution: Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery. Verapamil is excreted in human milk.

Excretion: Approximately 70% of an administered dose of verapamil is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3% to 4% is excreted in the urine as unchanged drug.

Special Populations and Conditions

Geriatrics: The pharmacokinetics of verapamil and trandolaprilat are significantly different in the elderly (≥65 years), compared to younger subjects. AUCs are increased approximately 80% with verapamil and 35% with trandolaprilat. In the elderly, verapamil clearance is reduced resulting in increases in elimination $t_{½}$ (see **WARNINGS AND PRECAUTIONS - Geriatrics**).

Hepatic Insufficiency: In patients with hepatic insufficiency, verapamil clearance is reduced by 30% and the elimination t½ is prolonged up to 14 to 16 hours (see **WARNINGS AND PRECAUTIONS - Use in Patients with Hepatic Impairment**, and **DOSAGE AND ADMINISTRATION**).

In patients with moderate to severe impairment of liver function, plasma trandolapril levels were approximately ten times higher than in healthy subjects. The plasma concentrations of trandolaprilat and the quantities excreted in the urine were also increased, although to a lesser degree. The dose should therefore be reduced in these patients.

In one study, cirrhotic patients who received a single dose of trandolapril 2 mg exhibited a 9-fold increase in trandolapril C_{max} and AUC values. The C_{max} and AUC values of trandolaprilat were about doubled.

Renal Insufficiency: The results of an intravenous pharmacokinetic study suggest that renal clearance of verapamil may be decreased in patients with renal disease (see **DOSAGE AND ADMINISTRATION**).

In patients with creatinine clearance $\leq$ 30 mL/min/1.73m^2, the C_{max} and AUC of trandolaprilat were approximately doubled after repeated oral administration of trandolapril, as compared to those of normal subjects.

STORAGE AND STABILITY

Store at 15 to 25°C (59 to 77°F). Protect from light and moisture. Do not use beyond the expiry date indicated on the label.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Verapamil, as the hydrochloride, is an almost white, bitter-tasting crystalline powder practically free from odour and readily soluble in chloroform and water (1 part in 20), but sparingly soluble in ethanol and practically insoluble in ether. It melts at 140°C and should be protected from light.

Trandolapril is a white crystalline powder with a melting point of approximately 125°C and a pKa=5.6. Practically insoluble in water, and freely soluble in chloroform, dichloromethane and methanol. It is free of odour with a bitter taste.

TARKA® sustained-release tablets are formulated for oral administration containing trandolapril in an immediate- release form and verapamil hydrochloride in a sustained-release formulation in five strength combinations: 1/180 mg; 2/180 mg; 1/240 mg; 2/240 mg: 4/240 mg.

TARKA® 1/180 mg sustained-release tablets are supplied as yellow, oval, film-coated tablets containing 1 mg trandolapril in an immediate-release form and 180 mg verapamil hydrochloride in a sustained- release form. The tablet is embossed with an arched triangle mark and “181".

TARKA® 2/180 mg sustained-release tablets are supplied as salmon, 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 embossed with an arched triangle mark and “182".

TARKA® 1/240 mg sustained-release 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 embossed with an arched triangle mark and “241".

TARKA® 2/240 mg sustained-release 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 embossed with an arched triangle mark and “242".

TARKA® 4/240 mg sustained-release 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 embossed with an arched triangle mark and “244".
Each TARKA® sustained-release tablet strength is available in bottles of 100 and 10 strips by 10 tablets of PVC/aluminum blisters.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

TARKA® (trandolapril/verapamil hydrochloride) is a combination of two active ingredients, verapamil hydrochloride and trandolapril:

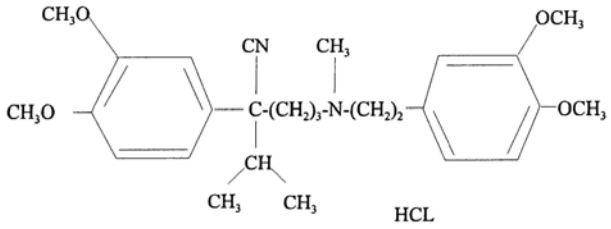
Proper name: Verapamil hydrochloride

Chemical name: ∝-isopropyl-∝ -[(N-methyl-N-homoveratryl)-γ-aminoropyl]-3,4-dimethoxyphenylaceto-nitrile hydrochloride

Molecular formula: $C_{27}H_{38}N_2O_4HCl$

Molecular mass: 491.08

Structural formula:



Physicochemical properties: Verapamil, as the hydrochloride, is an almost white, bitter-tasting crystalline powder practically free from odour and readily soluble in chloroform and water (1 part in 20), but sparingly soluble in ethanol and practically insoluble in ether. It melts at 140°C and should be protected from light.

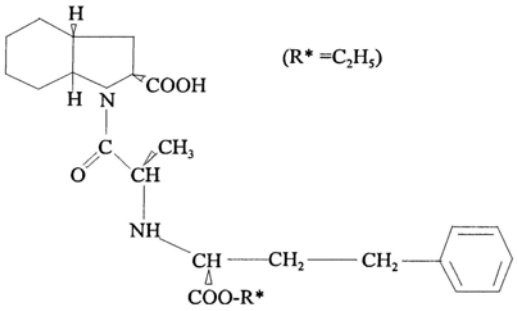
Proper name: Trandolapril

Chemical name: (2S, 3aR, 7aS)-1-[(S)-N-[(S)-1-(ethoxycarbonyl)-3-phenylpropyl] alanyl] hexahydro-2-indolinecarboxylic acid

Molecular formula: $C_{24}H_{34}N_2O_5$

Molecular mass: 430.5

Structural formula:



Physicochemical properties: Trandolapril is a white crystalline powder with a melting point of approximately 125°C and a pKa=5.6. Practically insoluble in water, and freely soluble in chloroform, dichloromethane and methanol. It is free of odour with a bitter taste.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

Verapamil reduces the open-state probability of the calcium channels in smooth muscle and myocardial cells, thus diminishing Ca++ influx via the slow channels. This, in turn, reduces vascular smooth muscle tone and myocardial contractility. In addition to this action, verapamil also delays AV conduction.

Trandolapril is transformed into the active diacid, trandolaprilat, by the action of esterases. It inhibits the action of angiotensin converting enzyme (ACE), thus preventing the conversion of angiotensin I, in itself inactive, into the potent vasoconstrictor, angiotensin II. Due to its inhibitory action on kininase II, it diminishes the rate of bradykinin inactivation, thus contributing toward a reduction in blood pressure.

To assess the interactions and advantages afforded by the combination of verapamil and trandolapril as opposed to the monosubstances, different dose combinations of the two components were tested for their antihypertensive and blood pressure lowering effects, and compared to corresponding doses of the substances given on their own.

Trandolapril/verapamil hydrochloride combinations ranging between 1:6.7 and 1:667 were tested orally in rats; in hypertensive dogs only the 1:1.9 combination was evaluated. In normotensive dogs the combinations 1:3.33 and 1:60 were tested orally. In the anaesthetized dog, the trandolapril/verapamil hydrochloride combination 1:2 was investigated via intravenous administration.

In both hypertensive and normotensive rats, the blood pressure lowering effect of the trandolapril/verapamil hydrochloride combination was found to be at least additive at all dose levels tested. The duration of action for the combination was also found to be superior to that of the monosubstances. Plasma level determinations performed in one study did not reveal any kinetic interactions between trandolapril and verapamil hydrochloride.

In the hypertensive dog, the effects of the combination were additive for all parameters measured. Blood pressure was decreased more prominently with the combination as compared to monotherapy. A greater blood pressure reduction efficacy of the trandolapril/verapamil hydrochloride combination as compared to the individual agents was also found in the normotensive dog following oral administration. After intravenous administration of trandolapril/verapamil hydrochloride to the anaesthetized dog, blood pressure was significantly reduced at doses which were not effective when the individual agents were administered alone.

Thus, the pharmacodynamic results available document at least an additive blood pressure lowering effect of the trandolapril/verapamil hydrochloride combination following administration at all dose levels tested in the rat and dog. There were no interactions observed between the calcium antagonistic effects and the ACE effects, as well as no pharmacokinetic interaction at these doses. Therefore, the superior efficacy of the combination in comparison to the individual agents is the result of a synergistic pharmacodynamic interaction at the target organs.

Metabolism

In vitro studies revealed that verapamil protein binding in rat and dog plasma was unaffected by the co-application of trandolapril or trandolaprilat, and that trandolaprilat plasma protein binding in the same species was not affected by the presence of verapamil. Furthermore, trandolaprilat did not affect the metabolism of verapamil by postmitochondrial superantant, nor did it influence the metabolism of verapamil by rat hepatocytes or in the isolated perfused rat liver. However, at high trandolaprilat concentrations, the microsomal metabolism of verapamil was inhibited.

In vivo, the pharmacokinetic profile of trandolapril/verapamil hydrochloride has been investigated in rats and dogs, the two animal species also included in pharmacological and toxicological studies. The principal objectives of the pharmacokinetic studies were to assess the pharmacokinetics of both components after combined administration and to investigate the potential for a pharmacokinetic interaction between the two components. These studies indicated a potential for the components to interact with each other, resulting in increased exposures after combined administration. This attained statistical significance in rats, but not in dogs. It is concluded that an increase in the fraction absorbed is the most probable explanation for this effect in rats, with verapamil as the target parameter, leaving unaffected those pharmacokinetic parameters that govern the disposition of a drug once it has entered the systemic circulation. From this it can be expected that in cases where absorption is complete or nearly so (e.g., lower verapamil doses), an interaction will be largely undetectable.

TOXICOLOGY

Acute Toxicity

Single dose toxicity studies were conducted in male and female mice and rats using trandolapril/ verapamil hydrochloride administered by oral and intraperitoneal routes. A summary of the LD_{50}'s determined in each of these studies is listed in table 6 below:

Table 6
Summary of LD_{50}s Obtained from Single-dose Toxicity Studies in Mice and Rats

Species	Sex	Route	Ratio T:V*	LD_{50} (mg/kg)
Mouse	M F	oral oral	1:60 1:60	158291
Mouse	M F	i.p. i.p.	1:60 1:60	71120
Rat	M F	oral oral	1:15 1:15	30892
Rat	M F	oral oral	1:60 1:60	159187
Rat	M F	oral oral	1:960 1:960	141119
Rat	M F	i.p. i.p.	1:60 1:60	2946
*T:V = trandolapril:verapamil hydrochloride				

The toxicity profile of the T/V combination was reflected in symptoms and signs lasting from 15 minutes up to 6 hours after administration. These symptoms and signs were dyspnea, spasmodic and/or frequent and forced respiration, prone and lateral position, piloerection, ptotic response, jumping and running fits, and weak gait following oral and intraperitoneal dosing of all trandolapril/verapamil hydrochloride mixtures. Additional symptoms and signs in the rat were diminished muscular tone and reduced grip strength, toe pinch and righting reflex with oral administration and opisthotonus with intraperitoneal injection. Symptoms and signs peculiar to the mouse were clonic convulsions. These symptoms are consistent with the known toxicity profile of verapamil.

Long-Term Toxicity

Verapamil hydrochloride

Subacute Toxicity

Oral Studies: Verapamil was administered orally in doses of 12.5, 25 and 50 mg/kg per day, to rats via food for 14 weeks (29 animals/group) and to dogs for 6 days/week in capsules, for 15 to 16 weeks (4 animals/group). Baboons received 2, 4, 8, 16, 32 and 64 mg/kg by mouth daily for 4 weeks (2 animals/group).

In rats, a dose-related increase in heart and lung weights was found. Dogs given 25 to 50 mg/kg showed slight weight loss and a significant reduction in heart rate up to week 11, followed by a gradual return to normal. In one dog on 12.5 mg/kg, one on 25 mg/kg and in all animals on 50 mg/kg, there was emesis during the first two weeks of the study. SGPT was elevated for one dog on 25 mg/kg at week 9 and for two animals on 50 mg/kg at the end of the test. Macroscopic examinations at necropsy were negative and there were no drug-attributable histological changes. The baboons showed no drug-related changes.

Intramuscular Studies: Beagle dogs were given 0, 2 and 10 mg/kg, 5 days/week for 30 days (4 animals/group). Injection sites in all animals became edematous and a dose-related reduction in heart rate was observed. At 10 mg/kg, hemoglobin and hematocrit values decreased and one animal had a raised SGPT. At necropsy, edema was noted at injection sites and higher spleen weights were recorded on the 10 mg/kg dose. One dog on this dose also showed increased inflammatory cell infiltration in the liver, with some hepatic cell degenerative changes.

Intravenous Studies: Verapamil was given to Sprague-Dawley rats at 0.2, 1 and 5.0 mg/kg once daily for 4 weeks (30 animals/group) and similarly to beagle dogs at 0.1, 0.4 and 1.6 mg/kg levels (6 animals/ group).

At the highest dose level, all dogs showed some restlessness, salivation and laboured breathing, along with delayed A-V conduction in one-half of the animals. In 4 of 6 animals at this highest dose (1.6 mg/ kg) sporadic small focal gatherings of Kupffer cells, with death of individual liver cells (necrobioses and/or necrosis of hepatocytes) were found histopathologically.

Chronic Toxicity

Oral: Rats were given verapamil at 10, 15, 25, 30, 60 and 62.5 mg/kg/day (50 animals/group) and beagle dogs at 10, 15, 25, 30, 40, 60, 62.5, 70, 81 and 85 mg/kg (6 animals/group) for 12 and 18 months. Clinical signs were observed and changes in food consumption, consistency of stools, hemograms, clinical chemistry and urinalyses performed. Blood pressure, ECG and ophthalmoscopic examinations were done on the dogs.

In one 18-month rat study, an increase in weight of the thyroid glands in females on the 62.5 mg dose was noted. In a later 12-month study, a slight reduction in weight gain was recorded.

In dogs, at doses of 60 mg and greater, toxic signs such as vomiting, salivation, reversible hyperplasia of the gums, reduced food consumption, slight weight loss and a transitory, slight to moderate elevation of SGPT were noted and three of the animals died. The 40 mg dose caused loss of coat colour and hair, and a delay in A-V conduction.

In another study, atypical lens changes (cataracts) were observed in 8 beagles receiving toxic dose levels (62.5 and 70 mg/kg). In a later study, 4 beagles were given 81 mg/kg for 18 months and none developed cataracts. It was concluded that any changes caused by verapamil in lens transparency are specific to the beagle. This is supported by the absence of similar lesions in other species studied, and by the apparent lack of any impairment by verapamil of carbohydrate or energy metabolism in lenticular tissue. The water-soluble proteins of the canine lens are known to have differences from those in other species.

Trandolapril

Trandolapril was administered orally to rats in doses up to 100 mg/kg/day for 30 days, 25 mg/kg/day for 6 months, and 9 mg/kg/day for 18 months. Dogs received oral doses of trandolapril up to 250 mg/kg/day for 30 days or 6 months, and up to 25 mg/kg/day for 12 months.

The principal signs seen in these repeat dose toxicity studies were of anaemia and renal effects (polyuria, polydipsia, increase in blood urea, creatinine and magnesium). These were more marked in the rat than in the dog. In addition, ulceration of the gastrointestinal tract was observed in dogs at doses above 125 mg/ kg/day for 6 months. Renal lesions for trandolapril were identified on histopathology as glomerulonephrosis in the rat (2.5 and 25 mg/kg/day for 6 months) and cortical tubular dilatation in the dog (25 to 250 mg/kg/day for 6 months). These effects were seen in the intermediate and high dose groups and were less marked in the longer term studies. Marginal biochemical indications of renal effects were seen at low doses (0.25 to 4 mg/kg/day).

Trandolapril/Verapamil Hydrochloride

A 13-week, oral (gavage), subchronic toxicity study was conducted in rats with the trandolapril/verapamil hydrochloride combination 1:120. Six treatment groups were evaluated: vehicle control, trandolapril control (0.333 mg/kg/day), verapamil hydrochloride control (40 mg/kg/day), and three groups of the trandolapril/verapamil hydrochloride combination (0.083/10, 0.167/20 and 0.333/40 mg/kg/day). The incidence of mortality observed in this study was generally low and did not exceed the 10% value reported for the verapamil control group.

There were no remarkable in-life or post-mortem findings that could be associated with the administration of trandolapril/verapamil hydrochloride. It was concluded that the trandolapril/ verapamil hydrochloride combination tested in this study did not produce any toxicologic findings which would be interpreted to be greater than that produced by the administration of verapamil alone at a dose of 40 mg/kg/day.

A 13-week, oral (capsule), subchronic toxicity study was also conducted in the beagle dog, in this case with a 1:60 trandolapril/verapamil hydrochloride combination. The seven treatment groups were as follows: control (placebo), trandolapril alone (0.8 mg/kg/day), verapamil alone (24 and 48 mg/kg/day), and three trandolapril/verapamil hydrochloride combination groups (0.2/12, 0.4/24 and 0.8/48 mg/kg/day). There were no deaths during the course of the study, and clinical signs were essentially restricted to the 48 mg/kg/day verapamil-containing groups with the more severe signs of erythema, salivation, uncoordinated movements, increased incidences of diarrhea, and convulsions in one dog, occurring in the highest dose trandolapril/verapamil hydrochloride group.

There were pronounced cardiac arrhythmias associated with a delay in atrioventricular conduction induced by all dosage levels of verapamil hydrochloride and the combination treatment, but not trandolapril alone. Liver involvement was indicated by increased alanine aminotransferase and/or ornithine carbamyltransferase plasma enzyme activity in all treated groups, with decreased plasma protein levels seen primarily in the treated groups receiving 48 mg/kg/day of verapamil hydrochloride.

Post mortem findings included increased heart weights for males treated with 48 mg/kg/day of verapamil hydrochloride alone or in combination with trandolapril, while female heart weights were increased only in the verapamil alone groups at 48 and 24 mg/kg/day. Likewise, slightly increased liver weights occurred in the dogs treated with the highest dose of verapamil. Histopathologically, there were no remarkable compound-related cellular changes seen in the heart, liver or any of the other organs examined.

Carcinogenicity

There was no evidence of a carcinogenic effect when verapamil hydrochloride was administered orally (diet) to male and female rats at doses up to 112.2 and 102.5 mg/kg/day, respectively, for 24 months, or when trandolapril was administered by gavage for 18 months to mice at doses up to 25 mg/kg/day and to rats at doses up to 8 mg/kg/day.

Mutagenicity

The mutagenic potential trandolapril/verapamil hydrochloride (1:60) was evaluated in four assays: the Salmonella/microsome (AMES) assay, the HPRT test on the V79 cell line, an *in vitro* chromosomal aberration test, and the chromosomal aberration test in the bone marrow of the Chinese hamster. The results obtained from these studies indicated that there were no gene mutations induced by the combination in any of the five salmonella typhimurium mutants or at the HPRT locus in V79 cells, and that the induction of structural chromosome aberrations and numerical aberrations by trandolapril/verapamil hydrochloride could be ruled out.

Reproduction and Teratology

Verapamil Hydrochloride

Studies were carried out in rats and rabbits with verapamil given in food and/or by gastric tube.

These studies included fertility and general reproduction performance in rats, teratogenicity studies in rats and rabbits and peri- and postnatal studies in rats. Rats were given 2.5, 12.5, 25 and 100 mg/kg body weight, by gastric tube and 1.3, 1.6, 5.2, 7.5, 13.3, 16 and 55 mg/kg body weight in food. In another teratogenicity study, rats were given 5, 10, and 20 mg/kg body weight by gavage three times daily at an interval of about 4.5 hours. Rabbits were given 5 and 15 mg/kg body weight by gastric tube.

There was no evidence of teratogenicity in either species and no embryotoxic effects observed in the rats dosed via food, or with doses up to 12.5 mg/kg body weight given by gastric tube, or with doses up to 10 mg/kg t.i.d. The single daily dose of 25 mg/kg body weight or more, caused a higher resorption rate in the rat. The dose of 20 mg/kg t.i.d. was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There was no difference in resorption rates observed in the rabbit and no effect on peri- and postnatal development or fertility in the rat.

Trandolapril

One Segment I reproductive toxicity study was conducted in rats, in which trandolapril was administered, by gavage, in doses up to 100 mg/kg/day to males for 60 days prior to mating, and to females for 14 days prior to mating until day 20 of gestation. Fetuses of females treated with 10 and 100 mg/kg/day showed dilated ureters and increased renal pelvic cavitation. A slightly increased incidence of incomplete ossification of thoracic vertebrae was also noted in these groups.

Four Segment II studies were also conducted. Trandolapril up to 1000 mg/kg/day was administered by gavage to rats during days 6 to 15 of gestation. At the highest dose administered to the dams, an increased incidence of dilatation of the renal pelvis and ureters over control values were observed in the fetuses.

In two studies, rabbits were administered trandolapril by gavage up to 0.8 mg/kg/day, during days 6 to 18 of gestation. In one of these studies (HYLA rabbits), maternal toxicity was observed in all treated groups, with marked lethality at the highest dose. An increased rate of fetal loss was seen at 0.1, 0.2 and 0.8 mg/kg/day in this study. No teratogenic effect was apparent in the surviving fetuses, although an increased incidence of renal pelvic dilatation was observed at 0.2 and 0.4 mg/kg/day. In the second study (New Zealand White rabbits), trandolapril 0.8 mg/kg/day was associated with maternal toxicity and mortality (12/21 dams). Pre- and post-implantation losses were also increased at this dose, as was the incidence of major malformations (skull, oral cavity, heart vessels). Dosing at 0.4 mg/kg/day in this study also resulted in a deterioration in maternal condition, but there were no consistent treatment-related effects on fetal development. At 0.2 mg/kg/day, slight effects on maternal condition were observed, but the developing fetus did not appear to be affected.

Female Cynomolgus monkeys were treated with trandolapril by intragastric intubation in doses up to 250 mg/kg/day, during days 20 to 50 of gestation. In one of the two studies conducted, there was no evidence of embryotoxicity or teratogenicity at the doses tested (50 and 250 mg/kg/day). In the second study, a slightly increased rate of abortions was seen at all doses (4 abortions at 10 and 50 mg/kg/day; 7 abortions at 125 mg/kg/day). There was also a slight decrease in mean fetal weight

at all doses. No treatment-related malformations were observed.

Trandolapril/Verapamil Hydrochloride

A study was performed in rats to ascertain the tolerability and relative toxicity of three dose levels of trandolapril/verapamil hydrochloride 1:120 (0.083/10, 0.166/20 and 0.333/40 mg/kg/day), two dose levels of verapamil hydrochloride alone (20 and 40 mg/kg/day) and one dose level of trandolapril alone (0.333 mg/kg/day). The treatments were administered to the females by gavage during days 6 to 15 of gestation. During the dosing period, food consumption and reduced body weight gains were seen in the dams of the high dose verapamil group, with and without trandolapril. Resorptions were significantly higher in the high dose trandolapril/ verapamil hydrochloride (14.3%), high dose trandolapril (10.2%) and the low dose verapamil groups (11.1%) compared to controls (5.5%). Fetal weights/litter were significantly lower only in the high dose trandolapril/verapamil hydrochloride group. Skeletal alterations were primarily found in the tails and toes. The tail findings were characterized by shortened, kinked or thread-like with agenesis of the sacral vertebrae. The toe findings were limited to perodactylia. Due to these unexpected observations, a second embryotoxicity and teratogenicity study was performed.

In the second Segment II study performed in female rats, trandolapril/verapamil hydrochloride 1:120 was administered by gavage during days 7 to 17 of gestation at dose levels of 0.083/10, 0.166/20 and 0.333/40 mg/kg/day. Verapamil hydrochloride alone at doses of 20, 40 and 60 mg/kg/day was administered in the same manner to three other treatment groups. The skeletal anomalies observed in the first study were not confirmed in this study. There was no evidence of teratogenicity, nor did any treatment significantly influence fetal development or functional behavioural parameters in two generations of progeny derived from treated dams. Fetal body weights were marginally reduced in the mid-dose combination group with slightly more reduction in the higher dose groups accompanied by a slight delay in skeletal ossification. There was an increased post-implantation loss rate with high dose verapamil hydrochloride alone (60 mg/kg/day).

REFERENCES

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PART III: CONSUMER INFORMATION

TARKA®
trandolapril/verapamil hydrochloride

This leaflet is part III of a three-part "Product Monograph" published when TARKA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TARKA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TARKA® is used to treat hypertension (high blood pressure).

What it does:
TARKA® contains two different types of medicines: a calcium channel blocker and an Angiotensin Converting Enzyme (ACE) inhibitor.

Calcium channel blockers change the amount of calcium getting into the muscle cells of your heart and blood vessels. This can change the strength and speed at which your heart beats. It also opens up the blood vessels so that blood can be pumped around your body more easily. This helps to lower your blood pressure.
ACE inhibitors also work by widening blood vessels, so helping to lower your blood pressure.

When it should not be used:
TARKA® should not be used if:
- you are allergic to any component of TARKA®, including active ingredients and non-active ingredients
- you are pregnant or breast feeding or
- you have certain serious heart conditions.

Ask your doctor for advice.

What the medicinal ingredient is:

TARKA® contains the ACE inhibitor trandolapril and the calcium channel blocker verapamil hydrochloride. The tablet consists of two layers, one layer containing trandolapril, and the other layer containing verapamil hydrochloride in a sustained-release matrix.

What the important non-medicinal ingredients are:
Corn starch, dioctyl sodium sulfosuccinate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, purified water, silicon dioxide, sodium alginate, sodium stearyl fumarate, synthetic iron oxides, talc, titanium dioxide.

What dosage forms it comes in:
TARKA is available as sustained-release tablets in the following strength combinations of trandolapril/verapamil hydrochloride:
1/180 mg; 2/180 mg; 1/240 mg; 2/240 mg; 4/240 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

TARKA® should not be used during pregnancy. If you discover that you are pregnant or if you are planning to become pregnant while taking TARKA, stop the medication and please contact your physician as soon as possible.

BEFORE you use TARKA® talk to your doctor or pharmacist if:
- you have any heart disease
- you have kidney disease
- you are taking beta-blockers;
- you have neuromuscular disease (i.e. myasthenia gravis or Duchenne muscular dystrophy);
- you have hepatic failure or elevated liver enzymes;
- you have allergies to this drug or any of its ingredients.

You are pregnant, breast-feeding or thinking of becoming pregnant? Taking TARKA®during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you become pregnant while taking TARKA® , stop the medication and report to your doctor as soon as possible. It is possible that TARKA® passes into breast milk. You should not breast-feed while taking TARKA®. If you need to keep breast-feeding, talk to your doctor about taking a different medicine to control your blood pressure.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with TARKA® include:

- Drugs used for the treatment of high blood pressure (hypertension) such as beta-blockers (e.g. propranolol, metoprolol);
- Drugs used for the treatment of abnormal heartbeats (arrhythmia) such as procainamide, flecainide, prazosin, terazosin, digoxin;
- Water tablets (diuretics) (e.g. hydrochlorothiazide) and potassium supplements (e.g. potassium chloride);
- Antibiotics such as erythromycin, telithromycin, rifampin;
- Some drugs used to treat diabetes (e.g. glyburide);
- Some drugs used to treat migraine headaches (e.g. almotriptan);
- Some drugs used to treat epilepsy or other neurological conditions (e.g. carbamazepine, phenobarbital);
- Some drugs used to treat stomach ulcers (e.g. cimetidine);
- Some drugs used to treat certain forms of arthritis or gout (e.g. sulfinpyrazone);
- Some drugs used to treat lung conditions such as asthma (e.g. theophylline);
- Any of the group of medicines known as major tranquilizers, or antidepressants of the tricyclic group (e.g. lorazepam, imipramine);
- Some drugs used to treat mood disorders (e.g. lithium);
- Any of the group of medicines known as non-steroidal anti-inflammatory drugs (e.g. naproxen, aspirin);
- Anti-cancer medications (e.g. cisplatin, doxorubicin);
- Any medication that can affect your immune system (e.g. corticosteroids, cyclosporine);
- Any neuromuscular blocking agent (e.g. atracurium)
- Some cholesterol lowering drugs (e.g., simvastatin, atorvastatin, lovastatin);
- Some HIV-antiviral medication (e.g. ritonavir);
- Grapefruit juice;
- Alcohol;
- St. John's Wort.

PROPER USE OF THIS MEDICATION

Usual dose:

Dosage must be individualized. The fixed combination is not for initial therapy. The dose of TARKA® should be determined by titration of the individual components. TARKA® should be taken once-a-day at the same time every day.

The usual adult dose for verapamil monotherapy is 180 to 240 mg/day.

The usual maintenance dose for trandolapril monotherapy is 1 to 2 mg once daily, as the recommended initial dose is 1 mg once daily.

Take TARKA® with food to help it work better. TARKA® sustained-release tablets should not be divided, crushed or chewed.

Overdose:

If you or someone you know accidentally takes more than stated dose, contact your doctor immediately or go to the nearest hospital with the tablets. Tell your doctor or hospital how much was taken. Treat even small overdoses seriously.

Missed Dose:

If you forget to take one tablet, take another as soon as you remember, unless it is almost time for your next dose. If it is, do not take the missed tablet at all.

Never double-up on a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its needed effects, a medicine may cause some unwanted effects. These are referred to as "side effects". Although not all of these side effects may occur, if they do occur they may need medical attention.

The most common side effects with TARKA® are dry cough, constipation and mild dizziness. Other less common side effects may include headaches, feeling sick (nausea), dry mouth, hair loss, nasal congestion, flushing of the face or neck, aches or pains in the joints of muscles, tiredness, swollen ankles, mild skin rash or itching, tingling or pickling of the skin, difficulty in sleeping, impotence, blurred vision, taste disturbance, anaemia or low numbers of white blood cells.

Check with your physician or pharmacist if you experience any unexpected effects, or are concerned by the above side effects.

SYMPTOMS OF SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	• Chest pain, faint pulse, irregular heartbeats		✓	✓
	• Fever and chills		✓	✓
	• Swelling of the face, mouth, tongue, trouble with swallowing or breathing		✓	✓
	• Dizziness, lightheadedness fainting		✓	✓

Check with your pharmacist or doctor **immediately**, if you experience any of the above symptoms of the serious side effects.

HOW TO STORE IT

Keep TARKA® and all other medicines out of reach of children.

TARKA® sustained-release tablets should be stored at 15˚C to 25˚C, protected from light and moisture.

Do not take your tablets after the expiry date shown on the label.

It is important to keep the TARKA® sustained-release tablets in the original package.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Health Canada
Address Locator: 0201C2
Ottawa, ON K1A 1B9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.abbott.ca or by contacting the sponsor, Abbott Laboratories, Limited, at: 1-800-361-7852

This leaflet was prepared by Abbott Laboratories, Limited.

Last revised: February 13, 2007