

PRODUCT MONOGRAPH

PrMAVIK[®]

trandolapril

0.5 mg, 1 mg, 2 mg and 4 mg Capsules

Angiotensin-Converting Enzyme Inhibitor

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MAVIK[®]

trandolapril

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsule / 0.5 mg, 1 mg, 2 mg and 4 mg	Erythrosine, gelatin, iron oxides and hydroxides, lactose, maize starch, povidone, sodium lauryl sulphate, sodium stearyl fumarate, titanium dioxide.

INDICATIONS AND CLINICAL USE

MAVIK[®] (trandolapril) is indicated for:

Essential Hypertension

- treatment of patients with mild to moderate essential hypertension. It may be used alone or in association with thiazide diuretics.

Trandolapril should normally be used in patients in whom treatment with a diuretic or a beta blocker was found ineffective or has been associated with unacceptable adverse effects.

Trandolapril can also be tried as an initial agent in those patients in whom use of diuretics and/or beta blockers are contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

The safety and efficacy of trandolapril in patients with renovascular hypertension has not been established, therefore its use in these conditions is not recommended.

Treatment Following Acute Myocardial Infarction

- following acute myocardial infarction in clinically stable patients with left ventricular dysfunction, with or without symptoms of heart failure, to improve survival and reduce hospitalizations for heart failure.

Sufficient experience in the treatment of patients with severe heart failure (NYHA Class IV) immediately after myocardial infarction is not yet available.

General

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

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 cannot be ruled out (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics**).

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

CONTRAINDICATIONS

MAVIK[®] (trandolapril) is contraindicated in patients who:

- are pregnant or planning to become pregnant.
- are hypersensitive to this drug 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.
- have a history of angioedema.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin converting enzyme (ACE) inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected or if the patient is planning to become pregnant, MAVIK[®] should be discontinued as soon as possible. See **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**.

Cardiovascular

Hypotension

Symptomatic hypotension has occurred after administration of MAVIK[®] (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 and salt 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 (see **ADVERSE REACTIONS**). 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. However, lower doses of trandolapril and/or reduced concomitant diuretic therapy should be considered.

If hypotension develops in patients receiving treatment following acute myocardial infarction, consideration should be given to discontinuation of trandolapril (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Treatment Following Myocardial Infarction, and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Treatment Following Myocardial Infarction**).

Aortic Stenosis

There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators.

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.

Endocrine and Metabolism

Hyperkalemia and Potassium-Sparing Diuretics

Increases in serum potassium (upper limit of normal range 5.0 mmol/L) were observed in approximately 2.2% of patients in clinical trials treated with trandolapril, in most cases these resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy in any hypertensive patient. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (see **DRUG INTERACTIONS**).

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

Patients with Impaired Liver Function

Trandolapril should be used with caution in patients with pre-existing liver abnormalities. In such patients, baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effect should apply.

Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug.

Elevations of liver enzymes and/or serum bilirubin have been reported with trandolapril (see **ADVERSE REACTIONS**). Should the patient receiving trandolapril experience any unexplained symptoms, particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigations be carried out. Discontinuation of trandolapril should be considered when appropriate. (See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Immune

Angioedema

Angioedema has been reported in patients taking ACE inhibitors, including MAVIK[®] (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.

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

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.

Peri-Operative Considerations

The hypotensive effects of certain inhalation anesthetics may be enhanced by ACE inhibitors. In patients undergoing surgery or anesthesia with agents producing 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 may be corrected by volume repletion.

Renal

Renal Impairment

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 MAVIK[®] (trandolapril) should include appropriate assessment of renal function.

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, MAVIK[®] 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.

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

Animal Data

Teratology studies in the rat were carried out at doses of 0, 100, 300, or 1000 mg/kg/day. An increased incidence of minor defects (dilation of renal pelvis and ureters) over control values was found at the 1000 mg/kg/day dose series. In fertility studies, where doses of 0, 1, 10 or 100 mg/kg/day were used, the incidence of pelvic cavitation and dilated ureters was increased with the 10 and 100 mg/kg/day dose. (See **TOXICOLOGY, Reproduction and Teratology**).

Teratology studies were carried out in the rabbit, both with and without electrolyte supplementation. In two studies without supplementation covering the 0.1 to 0.8 mg/kg dose range, maternal deaths were seen at all doses with a dose-related incidence. These were associated with fetal toxicity and increased fetal loss. No teratological effect was seen. Supplementation with electrolytes allowed doses of 2 to 8 mg/kg to be given: maternal toxicity was again seen, particularly at 8 mg/kg, with weight loss and abortion. No teratological effect was seen.

Two teratology studies were carried out in the cynomolgus monkey (doses of 0, 10, 50 or 250 mg/kg/day and also 5, 25 or 125 mg/kg/day): dosing was on days 20 to 50 of gestation with examination of the fetuses following caesarean section on day 100. Abortions were 3/10, 6/10, 5/11 and 7/10 at respectively 0, 10, 50 or 250 mg/kg/day and 1/10, 4/10, 4/10 and 7/10 at 0, 5, 25 or 125 mg/kg/day. Apart from one animal with a kinked tail in the group receiving 250 mg/kg/day, no other evidence of teratological effects attributable to treatment were observed.

Nursing Women: The presence of concentrations of ACE inhibitor has 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.

Pediatrics (< 18 years of age): The safety and effectiveness of trandolapril in children below the age of 18 have not been established. Therefore use in this age 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 cannot be ruled out (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics** and **Special Populations, Geriatrics**).

ADVERSE REACTIONS

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.

Essential Hypertension

The safety experience in double-blind, placebo-controlled and open-label studies includes 2581 patients with mild to moderate essential hypertension who received MAVIK[®] (trandolapril) therapy. Of these, 265 patients were 65 years of age or older. A total of 126 patients prematurely discontinued across the various trials due to adverse events. In long-term open-label trials, 1049 received trandolapril therapy, of which 212 continued treatment for 24 months, 689 for at least 12 months, and 911 for at least 6 months.

Severe adverse reactions occurring in long-term clinical trials (n=1049) with doses of trandolapril ranging from 0.5 mg to 8 mg included cough (3.9%), headache (2.3%), asthenia (2.1%), dizziness (1.7%), palpitations (0.7%), hypotension (0.5%), nausea (0.5%), pruritus (0.5%), and malaise (0.5%).

One serious adverse reaction was judged to be possibly related to trandolapril therapy. This involved a rapid supraventricular arrhythmia with atrial flutter which occurred in a 68 year old male patient with a known history of heart disease.

The adverse reactions (corresponding to possibly, probably or definitely related to treatment) with an incidence $\geq 1\%$ in all double-blind, placebo-controlled trials and open-label Phase 3 hypertension trials (n=2581) are shown in **Table 1**.

Table 1		
Adverse Reactions by Body System (SOC) Patients Receiving Trandolapril in Phase 3 Hypertension Trials $\geq 1\%$		
<i>Placebo-Controlled Studies</i>		
System Organ Class (SOC)	Trandolapril (n=693)	Placebo (n=194)
Nervous System Disorders		
Headache	2.31%	0.5%
Gastrointestinal Disorders		
Nausea	1.15%	0%
<i>Active-Controlled and Open-Label Studies</i>		
System Organ Class (SOC)	Trandolapril (n=1888)	
Nervous System Disorders		
Headache	2.17%	
Dizziness	1.59%	
Respiratory, Thoracic and Mediastinal Disorders		
Cough	2.60%	
General Disorders and Administration Site Conditions		
Asthenia	2.01%	

Treatment Following Acute Myocardial Infarction

In a survival study in patients with left ventricular dysfunction following myocardial infarction, 876 patients randomized to trandolapril, and 873 to placebo, were treated for an average of two years. A total of 209 patients prematurely discontinued across the various trials due adverse events.

The most serious adverse reactions occurring more frequently with trandolapril than with placebo included dizziness (2.6%) and hypotension (1.5%). The most frequent clinical adverse reactions occurring more frequently with trandolapril than with placebo were cough, dizziness and hypotension.

The adverse reactions (corresponding to possibly, probably or definitely related to treatment) with an incidence $\geq 1\%$, occurring in a higher percentage of trandolapril-treated patients than in placebo-treated patients, are presented in **Table 2**.

Table 2		
Adverse Reactions Reported With Trandolapril in Post Myocardial Infarction Patients in the TRACE Study That Occurred at a Frequency $\geq 1\%$		
System Organ Class (SOC)	Trandolapril (n = 876)	Placebo (n=873)
Nervous System Disorders Dizziness	1.9%	1.4%
Respiratory, Thoracic and Mediastinal Disorders Cough	3.9%	0.9%
Vascular Disorders Hypotension	2.1%	0.6%

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

Blood and Lymphatic

System Disorders:

anaemia, leukopenia, platelet disorder, thrombocytopenia, white blood cell disorder

Cardiac Disorders:

angina pectoris, bradycardia, cardiac failure, myocardial infarction, myocardial ischaemia, palpitations, tachycardia, ventricular tachycardia,

Congenital, Familial and

Genetic Disorders:

congenital arterial malformation, ichthyosis

Ear and Labyrinth Disorders:

vertigo, tinnitus

Eye Disorders:

abnormal vision, blepharitis, conjunctival oedema, eye disorder, glaucoma*, visual disturbance

Gastrointestinal Disorders:

abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, esophagitis*, flatulence, gastritis, gastrointestinal disorder, gastrointestinal pain, haematemesis, nausea, vomiting,

General Disorders and Administration site Conditions:	chest pain, fatigue, feeling abnormal, malaise, oedema, oedema peripheral
Hepatobiliary Disorders:	hepatitis, hyperbiliruninaemia
Immune System Disorders:	anaphylactoid reaction*, hypersensitivity
Infections and Infestations:	bronchitis, pharyngitis, upper respiratory tract infection, urinary tract infection
Injury, Poisoning and Procedural Complications:	injury
Metabolism and Nutritional Disorder:	anorexia, enzyme abnormality, gout, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hyperuricaemia, hyponatraemia
Musculoskeletal and Connective Tissue Disorders:	arthralgia, back pain, bone pain, muscle spasms, osteoarthritis, pain in extremity
Nervous System Disorders:	cerebrovascular accident, dysgeusia, migraine, migraine without aura, myoclonus, paresthesia, somnolence, syncope, tremor*
Psychiatric Disorders:	agitation, anxiety, apathy, depression, hallucination, insomnia, libido decreased, sleep disorder
Renal and Urinary Disorders:	azotaemia, pollakiuria, polyuria, renal failure
Reproductive System and Breast Disorders:	erectile dysfunction
Respiratory, Thoracic and Mediastinal Disorders:	dyspnoea, epistaxis, pharyngeal inflammation, pharyngolaryngeal pain, productive cough, respiratory disorder, upper respiratory tract congestion, upper respiratory tract inflammation

Skin and Subcutaneous

Tissue Disorders:

acne, angioneurotic oedema, dry skin, eczema, hyperhidrosis, pemphigus*, pruritus, psoriasis, rash, skin disorder

Vascular Disorders:

angiopathy, hot flush, hypertension, hypotension, orthostatic hypotension, peripheral vascular disorder, varicose vein

* These adverse effects represent adverse events; not reactions.

Rare cases of angioedema affecting the face, extremities, lips, tongue, glottis and/or larynx have been reported in patients treated with ACE inhibitor, including trandolapril.

A symptom complex has been reported which may include fever, vasculitis, myalgia, arthralgia/arthritis, a positive anti-nuclear antibody (ANA), elevated erythrocyte sedimentation rate (ESR), eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may also occur.

Rare report of increased appetite has been observed.

Abnormal Hematologic and Clinical Chemistry Findings

Clinical Laboratory Test Findings:

Blood creatinine increased, blood alkaline phosphatase increased, blood urea increased, blood lactate dehydrogenase increased, electrocardiogram abnormal, hyperkalaemia, hyperuricaemia, laboratory test abnormal, liver function test abnormal, platelet count decreased, transaminases increased.

Hematologic Findings:

Haematocrit decreased, haemoglobin decreased.

Post-Market Adverse Drug Reactions

System Organ Class	Adverse Event
Blood and Lymphatic System Disorders	Agranulocytosis, pancytopenia
Cardiac Disorders	Arrhythmia, cardiac arrest
Gastrointestinal Disorders	Abdominal pain, ileus, nausea
General Disorders and Administration Site Conditions	Fever
Hepatobiliary Disorders	Jaundice, pancreatitis
Musculoskeletal and Connective Tissue Disorders	Myalgia
Nervous System Disorders	Balance disorder, cerebral haemorrhage, dizziness, syncope, transient ischemic attack

System Organ Class	Adverse Event
Respiratory, Thoracic and Mediastinal Disorders	Angioedema, bronchospasm (cough, dyspnoea)
Skin and Appendages	Alopecia, leukocytoclastic vasculitis, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

DRUG INTERACTIONS

Drug-Drug Interactions

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.

Agents Causing Renin Release

The antihypertensive effect of trandolapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Alcohol

Alcohol enhances the bioavailability of ACE inhibitors.

Allopurinol, cytostatic, immunosuppressive agents, systemic corticosteroids or procainamide

Concomitant administration with ACE-inhibitors may lead to an increased risk of leukopenia.

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.

Antacids

They decrease the bioavailability of ACE inhibitors (it is recommended to ingest these products separately).

Concomitant Diuretic Therapy

Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy. The possibility of adverse hypotensive effects after the first dose of trandolapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with trandolapril. If it is not possible to discontinue the diuretic, the starting dose of trandolapril should be reduced and the patient should be closely observed for several hours following the initial dose until blood pressure has stabilized (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Digoxin

In one open-label study conducted in 8 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.

Lithium

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concurrently ACE inhibitors and lithium. 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.

Nifedipine SR

A study evaluating the potential pharmacokinetic and pharmacodynamic interaction between nifedipine (20 mg) (sustained release) and trandolapril (4 mg) was conducted in 12 healthy male volunteers. After a single dose, no pharmacokinetic or pharmacodynamic interaction was found between the two products.

Non-steroidal anti-inflammatory agents

The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of non-steroidal anti-inflammatory agents. As with other ACE inhibitors, the combination of

trandolapril with non-steroidal anti-inflammatory agents predisposes to a risk of hyperkalemia particularly in cases of renal failure.

Blood pressure should be monitored more closely when any NSAID is added or discontinued in a patient treated with trandolapril.

Warfarin

In a multi-dose, double-blind, placebo-controlled, pharmacodynamic interaction study with 20 healthy volunteers administered trandolapril (2 mg) and therapeutic doses of warfarin, no clinically significant effects on the anticoagulant properties of warfarin were found.

Drug-Food Interactions

Patients should be told not to use salt substitutes or foods containing potassium without consulting their physician (see **WARNINGS AND PRECAUTIONS**). Food does not affect the C_{max} and AUC of trandolapril and trandolaprilat, however food prolongs the T_{max} of trandolaprilat by approximately 2 hours.

Drug-Herb Interactions

Interactions with herbal products have not been evaluated.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been evaluated.

Drug-Lifestyle Interactions

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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Essential Hypertension

Dosage of MAVIK[®] (trandolapril) must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with trandolapril may need to be adjusted.

In some patients treated once daily, the antihypertensive effect may diminish towards 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 with trandolapril 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 (see **WARNINGS AND PRECAUTIONS**). 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.

Liver Impairment: A single oral dose of 2 mg of trandolapril was administered to patients with hepatic cirrhosis. Compared to healthy subjects receiving the same dose, C_{max} and AUC values of trandolapril increased by approximately 9 times; C_{max} and AUC of trandolaprilat were nearly doubled. (See **ACTION AND CLINICAL PHARMACOLOGY**, Pharmacokinetics and **WARNINGS AND PRECAUTIONS**, Hepatic/Biliary/Pancreatic, **Patients with Impaired Liver Function**).

Recommended Dose and Dosage Adjustment

Monotherapy

Adult: The recommended initial dosage of 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.

Dosage in the Elderly: In elderly patients with normal renal and hepatic function, no dosage adjustment is necessary (see **WARNINGS AND PRECAUTIONS**, **Geriatrics**).

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 m², 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 m²), a daily dosage of 0.5 mg in a single dose should not be exceeded.

Dosage in Liver Impairment: The recommended initial dose is 0.5 mg trandolapril once daily.

Treatment Following Acute Myocardial Infarction

Dosage should be individualized. Initiation of therapy requires consideration of concomitant medication and baseline blood pressure in hemodynamically stable patients.

A starting dose of 1 mg trandolapril once daily should be initiated no earlier than the third day following acute myocardial infarction in patients with left ventricular dysfunction.

After two days at 1 mg once daily, the dose should be increased to 2 mg once daily. For patients who cannot tolerate this dose, the 1 mg once daily dose can be maintained.

After one month, patients tolerating the 2 mg once daily dose should have their dosage increased to 4 mg once daily. Again, for patients who cannot tolerate the 4 mg once daily dose, the 2 mg once daily dose can be maintained.

The dose must be reduced when it is clinically necessary (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension**). If hypotension preventing the patient from standing or walking is observed and is not explained by other factors, the dose must be reduced.

For patients with renal or liver impairment, a starting dose no higher than 0.5 mg once daily should be instituted.

Missed Dose

If the patient forgets to take a capsule, he should take one as soon as he remembers, if he remembers on the same day. If not, he should not take the missed capsule at all. He should wait until it is time to take the next dose. He should never double-up on a dose to make up for the one he has missed.

Administration

Trandolapril may be taken before, during or after meals (see **DRUG INTERACTIONS, Drug-Food Interactions**).

OVERDOSAGE

Limited data are available regarding overdosage of MAVIK[®] (trandolapril) in humans. The most likely clinical manifestation of overdosage of an ACE inhibitor such as 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MAVIK[®] (trandolapril) is a non-sulphydryl angiotensin converting enzyme (ACE) inhibitor which is used in the treatment of mild to moderate essential hypertension and following acute myocardial infarction in clinically stable patients with left ventricular dysfunction.

Angiotensin-converting enzyme (ACE) is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the pharmacologically active substance, angiotensin II, which is a vasopressor agent. In addition, angiotensin II stimulates aldosterone secretion by the adrenal cortex. Inhibition of angiotensin-converting enzyme results in a decreased plasma angiotensin II level. The resulting lack of negative feedback on renal renin secretion leads to an increased plasma renin activity.

Angiotensin-converting enzyme is identical to kininase II. Thus, trandolapril administration may interfere with the degradation of the potent peptide vasodilator bradykinin, which may contribute to the therapeutic activity of trandolapril. Trandolapril is a prodrug, which is hydrolysed to its active diacid form, trandolaprilat, a potent ACE inhibitor.

The antihypertensive effect of trandolapril is due to a reduction in peripheral vascular resistance with little or no change in cardiac output and heart rate. The decrease in blood pressure is not accompanied by water or sodium retention. No modification was found in the urinary excretion of chloride and potassium. Administration of trandolapril to patients with essential hypertension results in reduction of both supine and standing blood pressure.

Pharmacodynamics

Administration of trandolapril to patients with mild to moderate essential hypertension results in a reduction of both supine and standing blood pressure usually with little or no orthostatic change or change in heart rate. Symptomatic postural hypotension is infrequent, although this may occur in patients who are salt- and/or volume-depleted (see **WARNINGS AND PRECAUTIONS**).

In mild to moderate hypertensive patients, significant reductions in blood pressure were seen at 2 hours, and peak antihypertensive effects were seen after approximately 8 hours. At the recommended doses, antihypertensive effects are maintained throughout the 24-hour dosing interval in most patients who responded to trandolapril. Abrupt withdrawal of trandolapril has not

resulted in rapid increase in blood pressure.

Following single oral therapeutic doses in healthy male volunteers, a rapid onset of ACE inhibition was observed. The peak inhibition was reached between 2 and 4 hours after the initial dose.

The effectiveness of trandolapril appears to be similar in the elderly (over 65 years of age) and younger adult patients given the same daily doses.

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

The antihypertensive effect of trandolapril and thiazide diuretics used concurrently is greater than that seen with either drug used alone.

Pharmacokinetics

Absorption: Following a single oral administration of trandolapril to healthy volunteers, trandolapril was detectable in the plasma 30 minutes later with peak concentrations reached within 1 hour. Trandolaprilat, the active metabolite, reached peak plasma concentrations after approximately 6 hours following trandolapril capsule administration. Plasma concentrations of both trandolapril and trandolaprilat were dose dependent. While food can delay the rate of absorption of trandolapril, there is no clinically significant effect on other pharmacokinetic and pharmacodynamic parameters of trandolaprilat.

Approximately 40 to 60% of an administered oral dose of trandolapril is absorbed.

Distribution: Eighty percent (80%) of the circulating trandolapril and up to 94% of the circulating trandolaprilat are bound to plasma proteins. The protein binding is not saturable for trandolapril but is saturable for trandolaprilat.

Metabolism: Trandolapril undergoes extensive first-pass metabolism in the liver, and this is the reason for its low bioavailability: 7.5% (ranging from 4 to 14%). In the liver it is transformed into its biologically active diacid form, trandolaprilat. Trandolaprilat itself is poorly absorbed after oral administration. 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.

Excretion: With once-daily dosing, a steady-state of trandolaprilat plasma concentrations is reached within 4 days in healthy male and female subjects as well as in patients with chronic renal failure. Similar results were found in young (< 65 years) as well as old (\geq 65 years) male and female patients suffering from mild to moderate essential hypertension. As is the case with several other ACE inhibitors, trandolaprilat has a polyphasic elimination profile with a slow terminal phase, probably the result of binding to ACE and a subsequently slow dissociation from the enzyme. Over the first 16 to 20 hours following oral administration of trandolapril, there is a rapid

elimination phase of trandolaprilat. Beyond this time, there is a prolonged terminal elimination phase. The effective half-life ($t_{1/2}$) for accumulation of trandolaprilat has been estimated to be in the range of 16 to 24 hours. The accumulation ratio as measured in hypertensive patients was about 1.5. Trandolapril's elimination half-life ($t_{1/2}$) is on average 0.7 hours.

In healthy male volunteers the excretion, in urine and feces, of trandolapril following an 8 mg single oral dose of ^{14}C -labelled drug is virtually complete after 7 days ($99.2 \pm 3.4\%$): eighty-two percent (82%) of the dose was eliminated in 48 hours and 93% of the dose in 72 hours. In this dual route of excretion, urinary and fecal recoveries accounted for 33% and 66% of the total excretion, respectively. Trandolaprilat represents 46% of the urinary and 57% of the fecal excretion. The glucuronide derivatives of trandolapril and trandolaprilat excreted represent each about 13% of total urinary excretion and, 2% and 4% of total fecal excretion. The diketopiperazine of trandolaprilat was 7% of the total urinary excretion. The amounts of trandolapril excreted unchanged and the corresponding diketopiperazine are negligible ($< 0.5\%$ of the dose).

Renal clearance of trandolaprilat varies depending on dose, as seen in **Table 3**. Trandolaprilat displays non-linear pharmacokinetics, especially at low doses.

Table 3				
Renal Clearance of Trandolaprilat after a Single Oral Administration of Trandolapril to Healthy Subjects				
Parameters	0.5 mg	1 mg	2 mg	4 mg
Trandolaprilat $\text{CL}_{\text{r}0-96\text{h}}$ (L/h)	0.15 ± 0.05	1.03 ± 0.18	2.02 ± 0.25	3.93 ± 0.39

Special Populations and Conditions

Pediatrics: Trandolapril pharmacokinetics have not been evaluated in patients less than 18 years of age.

Race: Pharmacokinetic differences have not been evaluated in different races.

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

STORAGE AND STABILITY

Store trandolapril between 15° and 25°C in original container. Trandolapril should not be stored beyond the date indicated on the container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Trandolapril capsules 0.5 mg, 1.0 mg, 2.0 mg and 4.0 mg contain the medicinal ingredient trandolapril in quantities of 0.5 mg, 1.0 mg, 2.0 mg and 4.0 mg respectively.

The qualitative formulation for all potencies of trandolapril is: trandolapril, maize starch, lactose, povidone and sodium stearyl fumarate (as filler and gliding agents), and empty gelatin capsules.

Empty gelatin capsules for all potencies of trandolapril are composed of gelatin NF and colouring agents specific to each potency (see **Table 4** below).

Potency	Cap	Body
0.5 mg	Titanium dioxide, Iron oxides and hydroxides, Sodium lauryl sulphate	Titanium dioxide, Iron oxides and hydroxides, Erythrosine, Sodium lauryl sulphate
1.0 mg	Titanium dioxide, Iron oxides and hydroxides, Erythrosine, Sodium lauryl sulphate	Titanium dioxide, Iron oxides and hydroxides, Erythrosine, Sodium lauryl sulphate
2.0 mg	Titanium dioxide, Iron oxides and hydroxides, Erythrosine, Sodium lauryl sulphate	Titanium dioxide, Iron oxides and hydroxides, Erythrosine, Sodium lauryl sulphate
4.0 mg	Titanium dioxide, Erythrosine, Iron oxide and hydroxides, Sodium lauryl sulphate	Titanium dioxide, Erythrosine, Iron oxide and hydroxides, Sodium lauryl sulphate

Availability of Dosage Forms

MAVIK[®] (trandolapril) is available in size no. 4 hard gelatin capsules in the following potencies (colours indicated in parentheses):

- 0.5 mg (red opaque body, yellow opaque cap)
- 1.0 mg (red opaque body, orange opaque cap)
- 2.0 mg (red opaque body, red opaque cap)
- 4.0 mg (red opaque body, brown opaque cap)

Trandolapril capsules 0.5 mg, 1.0 mg, 2.0 mg and 4.0 mg are available in HDPE plastic bottles of 100, or blister-packs of 28.

PART II: SCIENTIFIC INFORMATION

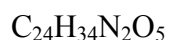
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Trandolapril

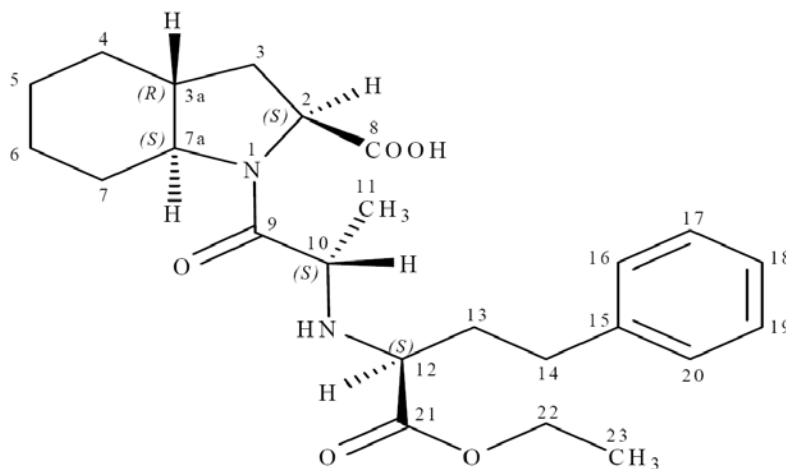
Chemical name: (2S, 3aR, 7aS)-1-[(S)-N-[(S)-1-(ethoxycarbonyl)-3-phenylpropyl]alanyl] hexahydro-2-indolinecarboxylic acid

Molecular formula and molecular mass:



430.5

Structural formula:



Physicochemical properties: 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.

CLINICAL TRIALS

Study Demographics and Trial Design

Hypertension

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 1	Multicentre, randomized, double-blind, placebo-controlled	0.5, 1 or 2 mg daily Oral dose 28 days	170 Placebo: 44 Trandolapril: 126	48.2 years (17 to 72)	Male: 66 Female: 104
Study 2	Multicentre, randomized, double-blind, placebo-controlled	0.25, 0.5, 1, 2 or 4 mg daily Oral dose 6 weeks	313 Placebo: 50 Trandolapril: 263	56.0 years (25 to 84)	Male: 203 Female: 110

Left Ventricular Dysfunction Following Acute Myocardial Infarction

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
TRACE*	Multicentre, randomized, double-blind, placebo-controlled	0.5 [†] , 1, 2, 4 mg daily Oral dose 24 to 50 months	1749 Placebo: 873 Trandolapril: 876	67.5 years (30 to 93)	Male: 1248 Female: 501

* TRACE: TRAndolapril Cardiac Evaluation study
† An oral test dose of 0.5 mg trandolapril was given to all eligible patients prior to randomization; patients were subsequently force-titrated to 1 to 4 mg per day.

Study Results

Hypertension

Studies 1 and 2 compared the efficacy and tolerance of trandolapril to placebo. Trandolapril administered once daily at doses of 1 mg, 2 mg and 4 mg for 4 to 6 weeks was effective at lowering average trough supine diastolic blood pressure in non-black patients with mild to moderate essential hypertension.

Left Ventricular Dysfunction Following Acute Myocardial Infarction

Primary Endpoints	Trandolapril	Placebo	p-Value
Mortality from all causes	304 (34.7%)	369 (42.3%)	p=0.001

It can be seen in **Table 7** and **Figure 1** that trandolapril provides a statistically significant reduction in death from all causes (final analysis of the intent-to-treat population).

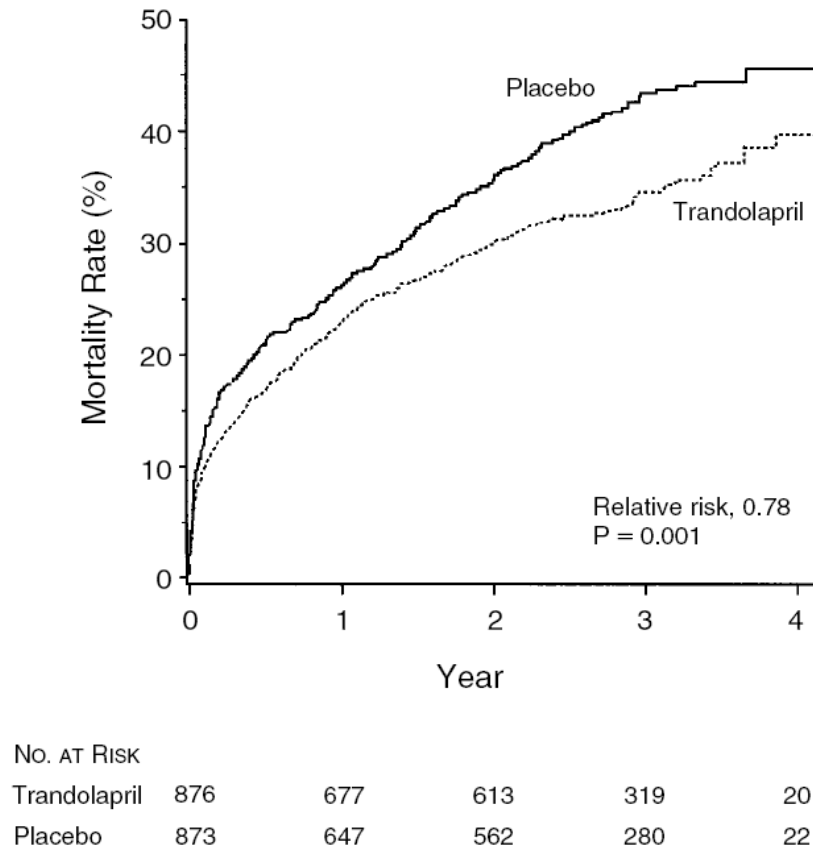


Figure 1. Cumulative Mortality from All Causes among Patients Receiving Trandolapril or Placebo

DETAILED PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

Table 8 summarizes the trandolapril mechanism of action in animal models.

Table 8 Trandolapril Mechanism of Action					
Study	Species	No. of animals per group	Route	Dose (mg/kg)	Results
Inhibition of Angiotensin I induced pressor response after oral trandolapril	Rat (Male) (Sprague Dawley)	4-9	Oral Single Dose	0.003 0.01 0.03 0.1 0.3	ID ₅₀ : trandolapril 35 mcg/kg trandolaprilat 500 mcg/kg
Inhibition of Angiotensin I induced pressor response after oral trandolapril	Dog Beagle	4	Oral	0.03 0.1 0.3 1.0	Dose dependent inhibition. At 0.3 mg/kg: 93% inhibition after 1.5 h and 29% after 6 h. At 1.0 mg/kg: 100% inhibition after 30 min and 59% after 6 h.
Effect of bilateral nephrectomy	Rat (spontaneously hypertensive)	10-11	Oral Single dose	3	The antihypertensive effect was abolished.
Effect of inhibition of prostaglandin biosynthesis (via Indomethacin 5 mg/kg p.o.)	Rat (spontaneously hypertensive)	10-11	Oral Single dose	3	The antihypertensive effect was not modified.
<i>In vitro</i> inhibition of ACE by trandolapril	Blood serum from Rat (Sprague Dawley) Dog (Beagle) Human (healthy male volunteers)	--	<i>In vitro</i>	--	Rat: IC ₅₀ = 1.67 ± 0.74 nM Dog: IC ₅₀ = 368 ± 50 nM Human: IC ₅₀ = 7.06 ± 2.11 nM

Table 8
Trandolapril Mechanism of Action

Study	Species	No. of animals per group	Route	Dose (mg/kg)	Results
Regional and general hemodynamic effects	Rat (spontaneously hypertensive)	10	Oral	5 (for 8 days)	On day 8 systolic blood pressure was reduced by 31% with no effect on heart rate, cardiac index and stroke volume. Total peripheral resistance was reduced by 37%. Regional vascular resistance was reduced in all territories (34-65%) whereas regional blood flow was increased in all regions explored (33-88%).
Determination of minimum effective dose	Rat (Male) (spontaneously hypertensive)	20	Oral	0.003 0.01 0.1 0.3 1.0 3.0 (for 14 days)	Dose dependent reduction in blood pressure; ranged from 8.5-39%. Dose dependent reduction in cardiac hypertrophy ranged from 5-17%.
ACE inhibition by measurement of the potentiation of the hypotensive response to bradykinin	Rat (Sprague Dawley) (Male)	6	i.v.	0.003 0.006 0.010 0.03 1 (single dose)	ED ₅₀ = Dose yielding 50% of the maximum increase in the hypotensive response to bradykinin Trandolapril = 4.9 mg/kg Trandolaprilat = 4.1 mg/kg
ACE inhibition in the rat aorta, atrium and ventricle	Rat (Okamoto) hypertensive (Male)	7-10	Oral	0.0001 0.0003 0.001 0.003 0.01 1.0	ID ₅₀ = Dose inhibiting enzyme activity by 50% Right atrium = 0.00132 Left atrium = 0.00107 Aorta = 0.00066 Apex = 0.00798 Right ventricular wall = 0.01510 Septum = 0.00740

Effects on Blood Pressure

Table 9 summarizes the effects of trandolapril on blood pressure in animal models.

Table 9						
Effects of Trandolapril on Blood Pressure						
Hypertensive Model	Species	No. of animals per group	Route	Dose (mg/kg)	Duration	Result
Antihypertensive effects in spontaneously hypertensive rats	Rat	12-22	Oral	0.3 3.0 30	Single dose	Fall in mean blood pressure 6 h after gavage: 10%, 13% and 17% at 0.3, 3.0 and 30 mg/kg, respectively. 24 h after gavage the fall was 10%, 11% and 15% at 0.3, 3.0 and 30 mg, respectively.
Antihypertensive effect in the spontaneously hypertensive rat pre-treated with a thiazide diuretic	Rat	12-22	Oral	0.3 3.0 30	Single dose	A dose-dependent fall in mean blood pressure of 14, 30 and 34% at doses of 0.3, 3.0 and 30 mg/kg, respectively was found. The peak effect occurred after 24 h.
Antihypertensive activity after 14 days of treatment in spontaneously hypertensive rats	Rat	11-12	Oral	3.0	14 days	Mean blood pressure decreased by 33% after 14 days.
Antihypertensive effect on conscious normotensive dog	Dog (Male Beagle)	5-6	Oral	3.0 10	Single dose	At 3 mg/kg: Diastolic blood pressure was reduced by 14% after 3.5-4 h post-administration. At 10 mg/kg: A decrease of 15% was observed 1.5-4 h post-administration

Pharmacokinetics

Table 10 summarizes the pharmacokinetic parameters following oral administration of trandolapril to animals and man.

		Rat	Dog	Man
Dose (mg/kg)		1	1	0.033
C _{max} (mcg/mL)	trandolapril	ND	0.05	0.002
	trandolaprilat	1.02	0.28	0.003
T _{max} (hr)	trandolapril	ND	0.77	0.5
	trandolaprilat	0.14	0.72	6
AUC (mcg·hr/mL)	trandolapril	ND	0.055	0.002
	trandolaprilat	0.47	0.46	0.046
T _{1/2} (hr)	trandolapril	ND	0.6	0.7
	trandolaprilat	6	1.6	3.5
% Bioavailability	trandolapril	ND	19	7.5
	trandolaprilat	37	43	40-60
% Elimination	bile	36	39	ND
	urine	18	16	33
	feces	36	40	66

TOXICOLOGY

Acute Toxicity

Table 11 summarizes the species-specific LD₅₀ values for both oral and intraperitoneal administrations of trandolapril.

Routes	Species	Sex	LD₅₀ (mg/kg)
Oral	Mouse	Male	4 875
		Female	3 990
	Rat	Male	> 5 000
		Female	> 5 000
Intraperitoneal	Mouse	Male	1 285
		Female	1 330
	Rat	Male	1 420
		Female	1 435

The symptoms observed in mice were: slight hypotonicity, pilo-erection, hunched back, motor incoordination, lethargy, locomotion difficulties, tremors. Deaths occurred within 48 hours after intraperitoneal administration and 3 hours after oral administration. Residual signs of toxicity persisted for a maximum of 3 days. On autopsy macroscopic examination revealed lesions of the liver, lungs and gastrointestinal tract. In rats, pilo-erection and epistaxis were the main clinical signs of toxicity after oral administration. After intraperitoneal administration clinical signs were similar to those found in mice. Autopsy findings included: lung congestion, hemorrhagic appearance of pancreas and internal wall of abdominal cavity, deformation of lobes of liver and hypertrophy of spleen and kidneys. A dose of 200 mg/kg in the dog caused the death of 2 animals out of 4, 24 hours after administration. Hypotonicity, hypomobility, dehydration and respiratory difficulties were observed in the surviving animals. Autopsy revealed hemorrhagic thymus lesions of the liver, lungs and gastrointestinal tract.

Chronic Toxicity

Table 12 summarizes the chronic toxicity results for oral administrations of trandolapril in animals.

Table 12					
Summary of Chronic Toxicity Results of Oral Administrations of Trandolapril in Animals					
Species	Duration	No. of animals per group	Route	Dose (mg/kg/day)	Effects
Rat Sprague Dawley	30 days	10 M, 10 F	Oral	0, 4, 20, 100	At all doses: Retardation of body weight gain, decrease in heart weight and gastric ulceration. At 20 and 100 mg/kg/day: Increase in magnesium and blood urea.
Rat Sprague Dawley	6 months	60 M, 60 F	Oral	0, 0.25, 2.5, 25	At all doses: Growth retardation, polyuria and polydipsia. At 2.5 and 25 mg/kg/day: Indications of glomerulonephritis were seen histologically particularly in males, which correlated with observed changes in serum magnesium urea and creatinine.
Rat Sprague Dawley	18 months	50 M, 50 F	Oral	0, 0.25, 1.5, 9	At 9 mg/kg: Water consumption, magnesium and urea increased. At 1.5 and 9 mg/kg: A decrease in sodium was noted. At 0.25 and 1.5 mg/kg in the males and at 9 mg/kg in females: Decrease in erythrocytes.
Dog Beagle	30 days	3 M, 3 F	Oral	0, 10, 50, 250	At all doses: Increase in urinary volume for females and microscopic renal lesions in all animals. At 250 mg/kg: Increase in serum alkaline phosphatase for males; increase in urea for all doses in females and at 50 and 250 mg/kg for males.

Species	Duration	No. of animals per group	Route	Dose (mg/kg/day)	Effects
Dog Beagle	6 months	9 M, 9 F	Oral	0, 2.5, 25, 125, 250	At all doses: Decreased excretion of sodium, potassium, chloride, calcium, magnesium and urea. At 250 and 125 mg/kg: digestive signs of toxicity accompanied by hypotonicity and dehydration resulted in death and premature sacrifice. Ulcerative inflammatory lesions of the gastric and duodenal mucosa, and renal lesions. Esophageal inflammatory lesions were also seen. At 25 mg/kg: Anemia, increase in frequency of renal lesions in the female.
Dog Beagle	12 months	6 M, 6 F	Oral	0, 0.25, 2.5, 25	At 0.25 mg/kg: Weight decrease in 3 animals between weeks 24 and 49. Decreases in spleen, kidney and testes weights in males. At 25 mg/kg: Increase in α_2 globulin in males. Decreases in absolute brain weights in males.

Reproduction and Teratology

Table 13 summarizes the reproduction and teratology results following administrations of trandolapril in animals.

Species	No. of animals per group	Dose (mg/kg/day)	Duration of dosing	Results
Rat (Sprague Dawley)	30 M, 30 F	0, 1, 10, 100	M: 60 days before mating F: 14 days before mating to day 30 of gestation	At 10 and 100 mg/kg/day: Fetuses showed dilated ureters and increased renal pelvic cavitation
Rat (Sprague Dawley)	24 F	0, 100, 300, 1000	Days 6-15 of gestation	Dilatation of renal pelvis and ureters at 1000 mg/kg/day.

Species	No. of animals per group	Dose (mg/kg/day)	Duration of dosing	Results
Rabbit (New Zealand White)	21 F	0, 0.2, 0.4, 0.8	Days 6-18 of gestation	At 0.8 mg/kg: Associated with maternal toxicity and severe effects on physical conditions of survivors, pre and post implantation losses were increased. Some fetuses had multiple malformations of the skull, oral cavity, heart vessels, etc. At 0.4 mg/kg: Deterioration in maternal condition, no consistent treatment-related effects on fetal development.
Rabbit (HYLA)	15 F	0, 0.1, 0.2, 0.4, 0.8	Days 6-18 of gestation	At 0.4 and 0.8 mg/kg: Weight loss, tremors, diarrhea and death, dilation of renal pelvis. At 0.1 and 0.2 mg/kg: Increased rate of fetal losses, dilation of renal pelvis.
Monkey (Cynomolgus)	6 F	0, 50, 250	Days 20-50 of gestation	At all doses: No sign of teratogenesis.
Monkey (Cynomolgus)	10 F	0, 5, 25, 125	Days 20-50 of gestation	At all doses: Slight decrease in body weight. No treatment related malformations. At 5 and 25 mg/kg: 4 abortions At 125 mg/kg: 7 abortions

Mutagenicity

Trandolapril was not mutagenic in the Ames microbial mutagen test, the gene conversion test with *S. cerevisiae*, and in V79 cells. Detection of chromosomal aberrations in human lymphocytes and in Chinese hamster CHO cells as well as the micronucleus test in mice were all negative.

Carcinogenicity

There was no evidence of a carcinogenic effect when trandolapril was administered by gavage for 18 months to male and female CDI mice at doses up to 25 mg/kg/day or to male and female Sprague Dawley rats at doses up to 8 mg/kg/day.

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PART III: CONSUMER INFORMATION**Pr MAVIK[®]
Trandolapril Capsules**

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

ABOUT THIS MEDICATION**What the medication is used for:**

MAVIK[®] is used to treat high blood pressure and is also used to treat patients after a heart attack.

Managing your lifestyle:

The "lifestyle" part of your treatment is as important as your medication. By working as a team with your doctor, you can help reduce the risk of hypertension complications to maintain the style of life you are accustomed to.

Together, you and your doctor can determine how each of the following applies to you:

Alcohol: Avoid alcoholic beverages until you have discussed their use with your doctor. Alcohol consumption may alter your blood pressure and/or increase the possibility of dizziness or fainting.

Diet: Generally, avoid fatty foods and food that is high in salt or cholesterol.

Exercise: Exercise regularly. It will help to keep your weight down, make you feel more energetic and is a good way to deal with stress. If you are not exercising regularly, be sure to discuss a fitness plan with your doctor.

Smoking: Avoid it completely.

What it does:

Your doctor has prescribed MAVIK[®], a medication that helps to control blood pressure. MAVIK[®] prevents blood vessels from constricting and therefore reduces blood pressure. It is not, however, a cure.

Although you may not feel any symptoms for years, hypertension can lead to stroke, heart attack, kidney disease and other serious conditions.

But it takes more than just medication to reduce blood pressure. Discuss the risk factors, and how they apply to your lifestyle, with your doctor. You may have to modify some of your daily habits to keep your blood pressure down.

Hypertension is the medical term for high blood pressure. When

blood flows through the blood vessels it pushes against their walls, almost like water pushing against the sides of a hose. Blood pressure is like that "push". When blood pressure is high (like the water pressure in a hose when the nozzle is partially shut), damage can occur to the heart and blood vessels.

When it should not be used:

MAVIK[®] should not be used if:

- you are pregnant or planning to become pregnant
- you are allergic to the drug or any non-medical ingredients
- you have a history of angioedema (disfiguring type of temporary swelling which can be hazardous, see Side Effects)

What the medicinal ingredient is:

Trandolapril

What the important nonmedicinal ingredients are:

Erythrosine, gelatin, iron oxides and hydroxides, lactose, maize starch, povidone, sodium lauryl sulphate, sodium stearyl fumarate, titanium dioxide.

What dosage forms it comes in:

MAVIK[®] is available in 0.5 mg, 1.0 mg, 2.0 mg and 4.0 mg capsules.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

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

BEFORE taking MAVIK[®], it is important that you inform your doctor or pharmacist of the following:

- You are taking salt substitutes or foods containing potassium. You should not be taking salt substitutes or foods containing potassium without the advice of your doctor.
- Other medical problems, especially if you have diabetes, liver disease, kidney disease, heart or blood vessel disease.
- You are pregnant, breast-feeding or thinking of becoming pregnant. Taking MAVIK[®] 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 MAVIK[®], stop the medication and report to your doctor as soon as possible. It is possible that MAVIK[®] passes into breast milk. You should not breast-feed while taking MAVIK[®] If you

need to keep breast-feeding, talk to your doctor about taking a different medicine to control your blood pressure.

- You are possibly allergic to MAVIK[®], including any of its non-medicinal ingredients.
- You are currently taking other medications. This is especially important if you are taking diuretics (water pills) which may add to the blood pressure lowering effect of MAVIK[®].
- You perform tasks which may require special attention (for example, driving an automobile or operating dangerous machinery). Almost all patients can, but you should not perform these tasks until you know how you tolerate your medicine.

If you are being treated for other conditions by other doctors, keep them all informed of which medications you are taking. Some drugs may reduce the effectiveness of MAVIK[®] or conversely, MAVIK[®] may reduce the effectiveness of other drugs.

If you have to undergo any dental or other surgery, inform the dentist or doctor in charge that you are taking this medication.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with MAVIK[®] include:

- Digoxin, lithium, nifedipine SR;
- Diuretics (water tablets) (e.g., hydrochlorothiazide);
- Potassium supplements, spironolactone, triamterene, amiloride;
- Any of the group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs);
- Any medication that can affect your immune system (e.g., corticosteroids).

PROPER USE OF THIS MEDICATION

Usual dose:

Most people with high blood pressure need to take only one MAVIK[®] capsule per day. You can take your medication with a meal, or if you prefer, on an empty stomach. It is important to take it at the same time every day as prescribed by your doctor.

Remember, hypertension is a long-term disease without short term symptoms. Just because you feel fine does not mean you can stop taking your medication. If you stop, serious complications of the disease may occur. Therefore, you should continue to take it regularly, as prescribed by your doctor.

With your first dose of MAVIK[®] your blood pressure may drop too low and you may experience a sensation of lightheadedness. Chances are that some of these side effects will disappear once your system becomes used to the medication. If they persist, discuss this with your doctor. Your medication may need to have the dose reduced or changed.

Overdose:

If you or someone you know accidentally takes more than stated dose, immediately contact the Regional Poison Control Centre, your doctor or go to the nearest hospital with the capsules. Tell your doctor or hospital how much was taken.

Overdose symptoms expected with drugs like MAVIK[®] include a severe drop in blood pressure, shock, stupor, and an abnormally slow heart beat.

Missed Dose:

If you forget to take one of your MAVIK[®] capsules, take one as soon as you remember, if you remember on the same day. If not, do not take your missed capsule at all. Simply wait until it is time for your next dose. Do not take two doses at once.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, any medication, including MAVIK[®], may cause side effects. After you have started taking MAVIK[®], it is important that you tell your doctor at once about any unexplained symptom you might experience.

Frequent side effects include coughing and dizziness. Other of occasional side effects include:

- **Headache**
- **Flu-like symptoms such as sore throat, fever, malaise, muscle pain, rash**
- **Nausea, vomiting, diarrhea**
- **Fatigue**
- **Sensation of lightheadedness**
- **Abdominal pain**
- **Loss of appetite (anorexia)**
- **Sad mood (depression)**

If you are suffering from excessive sweating, vomiting or diarrhea, your blood pressure may drop too low. If you feel ill after you have started taking MAVIK[®] capsules, or notice anything unusual or unexpected, tell your doctor or seek medical assistance.

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	
Common	Hypersensitivity reactions Skin rash, skin eruption or other effect of the skin or eyes, itching or fever			✓
	Hypotension Fainting when the blood pressure is too low			✓**
	Excess sweating, vomiting, diarrhea	✓		
	Palpitation Irregular or skipped heart beats		✓	
Uncommon	Allergic Reactions Swelling of the lips, face or neck, accompanied by difficulty breathing, speaking or swallowing (signs of angioedema†)			✓
	Jaundice Yellowing of the eyes and skin			✓
Frequency Not Known	Abdominal Pain (with or without nausea or vomiting)		✓	

* If you think you have these side effects, it is important that you seek medical advice from your doctor immediately.
 ** See PROPER USE OF THIS MEDICATION
 † Angioedema is characterized by swollen mouth, lips, tongue, eyes, extremities, throat or difficulty swallowing or breathing. Intestinal angioedema may also occur and is characterized by abdominal pain (with or without nausea or vomiting). **If you notice swelling or feel pain in these areas, inform your doctor immediately. You should also inform your doctor if you have unexplained fever, rash or itching.**

This is not a complete list of side effects. For any unexpected effects while taking MAVIK®, contact your doctor or pharmacist.

HOW TO STORE IT

Store MAVIK® between 15° and 25°C in original container. MAVIK® should not be stored beyond the date indicated on the container. Keep this drug out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

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

By toll-free telephone: 866-234-2345
 By toll-free fax: 866-678-6789
 Online: www.healthcanada.gc.ca/medeffect
 By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
 Tunney's Pasture, AL 0701C
 Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

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: 1-800-699-9948.

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