TARKA® 180/2

(Verapamil / Trandolapril)

NAME OF THE MEDICINAL PRODUCT

Tarka 180 mg/2 mg tablet

COMPOSITION

Each tablet contains 180 mg of verapamil hydrochloride and 2 mg of trandolapril.

PHARMACEUTICAL FORM

Modified- release tablet

CLINICAL PARTICULARS

Therapeutic indication

Essential hypertension in patients whose blood pressure has been normalized with the individual components in the same proportion of doses.

Posology and method of administration

The usual dosage is one tablet once daily taken in the morning half an hour before breakfast. The tablets should be swallowed whole. **Dosage in children:** Tarka is contraindicated in children and adolescents (<18 years) (See Contraindications). **Dosage in the elderly:** As systemic availability is higher in elderly patients compared to younger hypertensives, some elderly patients might experience a more pronounced blood pressure lowering effect (See Special Warnings and Precautions).**Dosage in renal failure:** Tarka is contraindicated in severe renal impairment (See Contraindications). **Dosage in hepatic insufficiency:** the use of Tarka is not recommended in patients with severe liver function impairment; Tarka is contraindicated in patients with liver cirrhosis with ascites (See Contraindications, and Special Warnings and Precautions)

Contraindications

Known hypersensitivity to trandolapril or any other ACE inhibitor and/or verapamil or to any of the excipients, history of angioneurotic edema associated with previous ACE inhibitor therapy, hereditary/idopathic angioneurotic edema, cardiogenic shock, recent myocardial infarction with complications, second - or third - degree AV block without pacemaker SA block, sick sinus syndrome, congestive heart failure, atrial flutter/fibrillation in association with an accessory pathway (e.g. WPW-syndrome), severe renal impairment (creat nine clearance < 10 ml/min), dialysis, liver cirrhosis with ascites, aortic or mitral stenosis, obstructive hypertrophic cardiomyopathy, primary aldosteronism, pregnancy lactation, use in children and adolescents (<18 years).

Special warnings and precautions for use

Symptomatic hypotens on:
Under certain circumstances, Tarka may occasionally produce symptomatic hypotension. This risk is elevated in patients with a stimulated renin- angiotensin-aldosterone system (e.g., volume or salt depletion, due to the use of diuretics, a low-sodium diet, dialysis, dehydration, diarrhea or vomiting; decreased left ventricular function, renovascular hypertension). Such patients should have their volume or salt depletion corrected before hand and therapy should preferably be initiated in a hospital setting. Patients experiencing hypotension during titration should lie down and may require volume expansion by oral fluid supply or intravenous administration of normal saline. Tarka therapy can usually be continued once blood volume and pressure have been effectively corrected.

Kidney function impairment (See also Contraindications):
Patients with moderate renal impairment should have their kidney function monitored.Tarka may produce hyperkalemia in patients with renal dysfunction. Acute deteriorationof kidney function (acute renalfailure)may occurespecially inpatientswith pre-existing kidney function impairment, or congestive heartfailure.There is no sufficient experience with Tarka in secondary hypertension and particularly in renal vascular hypertension. Hence, Tarka should not be administered to these patients, especially since patients with bilateral renal artery stenosis or unilateral renal artery stenosis in individuals with a single functioning kidney (e.g., renal transplant patients) are endangered to suffer an acute loss of kidney function.

Proteinuria:
Proteinuria may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

Severe liver function impairment:
Since there is no sufficient therapeutic experience in those patients, the use of Tarka cannot be recommended. Tarka is contraindicated in patients with liver cirrhosis with ascites (See also Contra ndications).

Angioneurotic edema:
Rarely, ACE inhibitors (such as trandolapril) may cause angioneurotic edema that includes swelling of the face, extremities, tongue, glottis, and/or larynx. Patients experiencing angioneurotic edema must immediately discontinue trandolapril therapy and be monitored until edema resolution. Angioneurotic edema confined to the face will usually resolve spontaneously. Edema involving not only the face but also the glottis may be life threatening because of the risk of airway obstruction. Compared to non-black patients a higher incidence of angioedema has been reported in black patients treated with ACE inhibitors . Angioneurotic edema involving the tongue, glottis or larynx requires immediate subcutaneous administration of 0.3-0.5 ml of epinephrine solution (1:1000) along with other therapeutic measures as appropriate. Caution must be exercised in patients with a history of idiopathic angioneurotic edema, and Tarka is contraindicated if angioneurotic edema was an adverse reaction to an ACE inhibitor (See also Contra-indications)

Neutropenia/agranulocytos s
The risk of neutropenia appears to be dose- and type-related and is dependent on patient's clinical status. It is rarely seen in uncomplicated patients but may occur in patients with some degree of renal impairment especially when it is associated with collagen vascular disease e.g. systemic lupus erythematosus, scleroderma and therapy with immunosuppressive medicinal products. It is reversible after discontinuation of the ACE inhibitor

Cough:
During treatment with an ACE inhibitor a dry and non-productive cough may occur which disappears after discontinuation.

Hyperkalaemia:
Hyperkalemia may occur during treatment with an ACE inhibitor, especially in the presence of renal insufficiency and/or heart failure. Potassium supplements or potassium sparing diuretics are generally not recommended, since they may lead to significant increases in plasma potassium. If concomitant use of the above mentioned medicinal products is deemed appropriate, they should be used with frequent monitoring of serum potassium.

Elderly:
Tarka has been studied in a limited number of elderly hypertensive patients only Pharmacokinetic data show that the systemic availability of Tarka is higher in elderly compared to younger hypertensives. Some elderly patients might experience a more pronounced blood pressure lowering effect than others. Evaluation of the renal function at the beginning of treatment is recommended.

Surgical patients:
In patients undergoing major surgery requiring general anesthesia, ACE inhibitors may produce hypotension, which can be corrected by plasma volume expanders.

Conduct on d sturbances:
Treatments should be used with caution in patients with first-degree atrioventricular block (See also Contraindications).

Bradycardia:
Tarka should be used with caution in patients with bradycardia.

Diseases in which neuromuscular transm ss on is affected:
Tarka should be used with caution in patients with diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert- Eaton syndrome, advanced Duchenne muscular dystrophy).

Hemodialysis patients (See also Contraindications)
Patients on concurrent ACE inhibitor therapy and hemodialysis with polyacrylonitrile methallyl sulfonate high-flux membranes (e.g. 'AN 69') have experienced anaphylactoid reactions. Such membranes should therefore not be used in these patients.

Desensitizat on:
Anaphylactoid reactions (in some cases life threatening) may develop in patients receiving ACE inhibitor therapy and concomitant desensitization against animal venoms.

LDL-apheresis:
Life threatening anaphylactoid reactions have been noted when patients on LDL-apheresis take ACE inhibitors at the same time. Evaluation of the patients should include assessment of renal function prior to initiation of therapy and during treatment. Blood pressure readings for evaluation of therapeutic response to Tarka should always be taken before the next dose.

Lactose
Tarka tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapplactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains 1.12 mmol (or 25.76 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

Interaction with other medicinal products and other forms of interaction

Not recommended association
- Potassium sparing diuretics or potassium supplements: ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spironolactone, triamterene, or amiloride, potassium supplements, or potassium containing salt substitutes may lead to significant increases in serum potassium, particularly in the presence of renal function impairment. If concomitant use is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.
- The simultaneous use of verapamil with dantrolene is not recommended.

Precaution for use
- Antihypertensive medicinal products: increase of the hypotensive effect of Tarka.
- Diuretics: patients on diuretics and especially those whoare volume- and / or salt depleted may experience an excessive reduction of blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to intake and by initiation of therapy with low doses. Further increases in dosage should be performed with caution.
- Lithium: there have been reports of both an increase and a reduction in the effects of lithium used concurrently with verapamil. The concomitant administration of ACE inhibitors with lithium may reduce the excretion of lithium. Serum lithium levels should be monitored frequently
- Anaesthetics: Tarka may enhance the hypotensive effects of certain anaesthetic medicinal products
- Narcotics/antipsychotics: postural hypotension may occur
- Allopurinol, cytostatic or immunosuppressive medicinal products, systemic corticosteroids or procainamide: concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.
- Cardiodepressive medicinal products: the concurrent use of verapamil and cardiodepressives, i.e., medicinal products that inhibit cardiac impulse generation and conduction (e.g., beta- adrenergic blockers, antiarrhythmics, inhalation anesthetics), may produce undesirable additive effects.
- Quinidine: the concomitant use of quinidine and oral verapamil in patients with hypertrophic (obstructive) cardiomyopathy has resulted in hypotension and pulmonary edema in a small number of cases.
- Digoxin: concurrent use of digoxin and verapamil has been reported to result in 50-75% higher digoxin plasma concentrations, requiring reduction of the digoxindosage.
- Muscle relaxants: the effect of muscle relaxants may be enhanced.
- Tranquilizers/antidepressants: as with all antihypertensives, there is an elevated risk of orthostatic hypotension when combining Tarka with major tranquilizers or antidepressant medicinal products containing imipramine.

Take into account
- Non-steroidal anti- inflammatory drugs: the administration of a non-steroidal anti-inflammatory medicinal product may reduce the antihypertensive effect of an ACE inhibitor Furthermore it has been described that NSAIDs andACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. These effects are in principle reversible, and occur especially in patients with compromised renal function.
- Antacids: induce decreased bioavailability of ACE inhibitors.
- Sympathomimetics: may reduce the antihypertensive effects of ACE inhibitors; patient should be carefully monitored to confirm that the desired effect is being obtained.
- Alcohol: enhances the hypotensive effect.
- Verapamil may increase the plasma concentrations of carbamazepine, cyclosporin, and theo-phylline.
- Rifampin, phenytoin, and phenobarbital reduce the efficacy of verapamil, whereas cimetidinemay increase the effect of verapamil.
- Antidiabetics: a dose adjustment of antidiabetics or of Tarka may be necessary in individual cases especially at the start of therapy due to increased reduction of blood glucose.
- Grape fruit juice has been shown to increase the plasma levels of verapamil, which is a component of Tarka. Grape fruit juice should therefore not be ingested with Tarka.
- Food has been shown to decrease the rate but not the extent of absorption of verapamil. It is therefore recommended to take the medicinal product half an hour before breakfast (See Posology and Methods of Administration).

Pregnancy and Lactation

Pregnancy
The safe use of Tarka in pregnant women is inadequately documented. However, there have been anecdotal reports of neonatal lung hypoplasia, intra-uterine growth retardation, persistent ductus arteriosus, and cranial hypoplasia following exposure of fetuses to ACE inhibitors. In addition, the pharmacologic activity of ACE inhibitors is compatible with the possibility of fetal hypotension, which may be associated with fetal/neonatal oliguria/anuria and oligohydramnios. Teratogenic effects are primarily expected when ACE inhibitors are used in the second and third trimesters of pregnancy, and it is not known whether exposure of the embryo/fetus to an ACE inhibitor only in the first trimester is teratogenic or embryotoxic/fetotoxic. Women who wish to get pregnant or are pregnant must consult their doctor without delay, so an alternative pharmacologic treatment can be prescribed. Doctors should instruct women of child-bearing potential accordingly before prescribing an ACE inhibitor.

Lactation
Tarka is contraindicated when breastfeeding.

Effects on ability to drive and use machines:
While no effect on the ability to drive and use machinery has been established, impairment of alertness cannot be ruled out altogether, since Tarka may produce dizziness and fatigue.

Undesirable effects

The adverse drug reactions for Tarka are consistent with those known for its components or the respective class of medicinal products. The most commonly reported adverse drug reactions are cough, headache, constipation, vertigo dizziness and hot flushes (see table below). Adverse events either reported spontaneously or observed in clinical trials are depicted in the following table. Within each system organ class, the ADRs are ranked under headings of frequency using the following convention: common (>1/100 and <1/10), uncommon (>1/1.000 and <1/100), rare (>1/10.000 and <1/1.000), very rare (<1/10,000), including isolated reports.

System Organ Class	Frequency	Undesirable Effects
Blood and lymphatic system disorders	very rare	- leukopenia - pancytopenia - thrombocytopenia
Immune system disorders	very rare	- allergic reaction, unspecified - increase in gammaglobulin - hypersensitivity, unspecified
Metabolism and nutritional disorders		- hyperlipidaemia - anorexia
Psychiatric disorders	very rare	- somnolence - aggression - anxiety - depression - nervousness
Nervous system disorders	uncommon rare very rare	- dizziness - vertigo - tremor - collapse - impaired balance - insomnia - paresthesia or hyperesthesia - syncope or acute circulatory failures with loss of consciousness - taste aberration - weakness
Eye disorders		- abnormal/blurred vision
Cardiac disorders/ vascular disorders	veryrare	- hot flushes - AV block, first degree - palpitation - angina pectoris - atrial fibrillation - AV block, complete - AV block, unspecified - bradycardia - cardiac arrest - cerebral hemorrhage - edema, peripheral - edema, unspecified - flushing - heartfailure - hypotensive events including orthostasis or fluctuation of blood pressure (see special warnings & precautions) - tachycardia
Respiratory thoracic and mediastenal disorders	very rare	- cough - asthma - bronchitis - dyspnea - sinus congestion

Gastrointestinal disorders		- constipation - abdominal pain - diarrhea - gastrointestinal disorders, unspecified - nausea
	very rare	- dry mouth/throat - pancreatitis - vomitin
Hepatobiliary disorders		
	veryrare	- cholestasis - hepatitis - increase in GT - increase in LDH - increase in lipase - jaundice
Skin and subcutaneous tissue disorders		- facial edema - pruritus - rash - sweating increased - alopecia - herpes simplex - skin disorders, unspecified
	veryrare	- angioneurotic edema (see special warnings & precautions) - erythema multiforme - exanthema or dermatitis - psoriasis - urticaria
Musculoskeletal, connective tissue and bone disorders	veryrare	- arthralgia - myalgia - myasthenia
Renal and urinary disorders		- polyuria
	veryrare	- acute renal failure(see special warnings & precautions)
Reproductive system and breast disorders	veryrare	- gynecomastia - impotence
General disorders and administration site conditions		- headache - chestpain
	veryrare	- fatigue or asthenia
Investigations		- liver function test, abnormal - hyperbilirubinemia
	veryrare	- increase in alkaline phosphatase - increase in serum potassium - increase in transaminases

The following adverse reactions have not yet been reported in relation to Tarka, but are generally accepted as being atributable toACE inhibitors

- Blood and lymphatic system disorders: decreases in hemoglobin and hematocrit, and in individualcases agranulocytosis. Isolated cases of hemolytic anemia have been reported in patients with congenital G-6-PDH deficiency
- Psychiatric disorders: occasionally confusion.
- Nervous system disorders: rarely sleep disorders.
- Ear and labyrinth disorders: rarely problems with balance, tinnitus.
- Cardiac disorders/vascular disorders: Individual cases of arrhythmia, myocardial infarction and transient ischemicattacks have been reportedforACE inhibitors in association with hypotension.
- Respiratory thoracic and mediastinal disorders: Rarely sinusitis, rhinitis, glossitis, and bronchospasm.
- Gastrointestinal disorders: occasionally indigestion. Individual casesof ileus.
- Hepatobiliary disorders: individual casesof cholestaticicterus.
- Skin and subcutaneous tissue disorders: occasionally allergic and hypersensitivity reactions such as Stevens-Johnson syndrome, toxic epidermic necrolysis. This can be accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased ANA- titers.
- Investigations: increases in blood urea and plasma creatinine may occur especially in thepresence of renal insufficiency severe heart failure and renovascular hypertension. These increases are however reversible on discontinuation.

Symptomatic or severe hypotension has occasionally occurredafter initiation of therapy with ACE inhibitors. This occurs especially in certain risk groups, such as patients with a stimulated rennin-angio tensin-aldosteronesystem.

The following adverse reactions have not yet been reported in relation to Tarka, but are generally accepted as being at ributable to phenylalkylamine calcium-channel blockers

- Nervous system disorders: in some cases, there may be extrapyramidal symptoms (Parkinson's disease, choreoathetosis, dystonicsyndrome). Experience so far has shown that these symptoms resolve once the medicinal product is discontinued. There have been isolated reports of exacerbation of myasthenia gravis, Lambert- Eaton syndrome and advanced cases of Duchenne's muscular dystrophy
- Gastrointestinal disorders: gingival hyperplasia following long-term treatment is extremely rareand reversible after discontinuation of therapy.
- Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome and erythromelalgia have been described. In isolated cases allergic skin reactions like erythema.
- Reproductive system and breast disorders: Hyperprolactinemia and galactorrhea have been described.

Excessive hypotension in patients with angina pectoris or cerebrovascular disease treated with Verapamil may result in myocardial infarction or cerebrovascular accident.

Overdose

There have as yet been no reports of overdosage with the combination product. The highest dose used in clinical trials was 16 mg of trandolapril. This dose produced no signs or symptoms of intolerance. The most important symptom to be expected after a significant overdose is hypotension. Administration of normal saline solution is recommended in this case. The most important signs and symptoms of a verapamil overdose are due to its pharmacologic activity in the cardiovascular system and include hypotension arising from peripheral vasodilation and a negative inotropic effect, depression of impulse generation in the sinus node and cardiac impulse conduction disturbances that may result in sinus bradycardia, sinus arrest, AV block, and asystole. Following oral verapamil overdosage, the patient must be monitored and treated in an intensive care setting. Overdose management must be aimed at preventing the further absorption of verapamil from the gastrointestinal tract, providing symptomatic treatment of the toxic effects (see above), and compensating for the calcium-antagonistic effects of this active substance. Further absorption of verapamil from the gastrointestinal tract can be prevented by gastric lavage, administration of adsorbent material (activated charcoal) and a cathartic (sodium sulfate). Apart from general supportive measures in response to severe hypotension (to the point of shock), i.e., maintenance of an adequate circulating blood volume by administering plasma or a plasma expander it may be necessary to stimulate the heart muscle with such positive inotropic medicinal products as dopamine, dobutamine or isoproterenol. Atropine (or methylatropine) may be useful in the management of sinus bradycardia. AV block should be treated with sympathomimetic medicinal products (isoproterenol or metaproterenol) or a pacemaker. Asystole should be handled by the usual measures including cardiopulmonary resuscitation, cardiac pacing, etc. The calcium-antagonistic effect can be offset by parenteral administration of calcium, for instance as calcium gluconate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Tarka is a fixed combination of the heart-rateloweringcalcium antagonist verapamil and the ACE inhibitor trandolapril.

Verapamil

The pharmacologic action of verapamil is due to inhibition of the influx of calcium ions through the slow channels of the cell membrane of vascular smooth muscle cells and of the conductile and contractile cells in the heart.

The mechanism of action of verapamil produces the following effects:

1. Arterial vasodilation.

Verapamil reduces arterial pressure both at rest and at a given level of exercise by dilating peripheral arterioles. This reduction in total peripheral resistance (afterload) reduces myocardial oxygen requirements and energy consumption.

2. Reduction of myocardial contractility.

The negative inotropic activity of verapamil can be compensated by the reduction in total peripheral resistance. The cardiac index will not be decreased unless in patients with preexisting left ventricular dysfunction.

Verapamil does not interfere with sympathetic regulation of the heart because it does not block the beta-adrenergic receptors. Spastic bronchitis and similar conditions, therefore, are not contraindications to verapamil.

Trandolapril

Trandolapril suppresses the plasma renin-angiotensin-aldosterone system (RAS). Renin is an endogenous enzyme synthesized by the kidneys and released into the circulation where it converts angiotensinogen to angiotensin I a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme, a peptidyldipeptidase, to angiotensin II. Angiotensin II is a potent vasoconstrictor responsible for arterial vasoconstriction and increased blood pressure, as well as for stimulation of the adrenal gland to secrete aldosterone. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to reduced aldosterone secretion. Although the later decrease is small, small increase in serum potassium concentrations may occur along with sodium and fluid loss. The cessation of the negative feedback of angiotensin II on the renin secretion results in an increase of the plasma renin activity. Another function of the converting enzyme is to degrade the potent vasodilating kinin peptide bradykinin to inactive metabolites. Therefore inhibition of ACE results in an increased activity of circulating and local kallikrein-kinin system which contributes to peripheral vasodilation by activating the prostaglandin system. It is possible that this mechanism is involved in the hypotensive effects of ACE inhibitors and is responsible for certain adverse reactions. In patients with hypertension administration of ACE inhibitors results in a reduction of supine and standing blood pressure to about the same extent with no compensatory increase of the heart rate. Peripheral arterial resistance is reduced with either no change or an increase in cardiac output. There is an increase in renal blood flow and glomerular filtration rate is usually unchanged. Achievement of optimal blood pressure reduction may require several weeks of therapy in some patients. The antihypertensive effects are maintained during long term therapy Abrupt withdrawal of theapy has not been associated with a rapid increase in blood pressure. The anti-hypertensive effect of trandolapril sets in one hour post-dose and lasts for at least 24 hours, but trandolapril does not interfere with the circadian blood pressure pattern.

Tarka

Neither animal studies nor healthy volunteer studies could demonstrate pharmacokinetic or RAS interactions between verapamil and trandolapril. The observed synergistic activity of these two active substances must therefore be due to their complementary pharmacodynamic actions. In clinical trials Tarka was more effective in reducing high blood pressure than either active substance alone. In longterm trials, Tarka proved to be safe and well tolerated.

Pharmacokinetic properties

Tarka tablets are film-coated and composed of a layer designed for sustained release of verapamil hydrochloride and a separate layer intended for immediate release of trandolapril.

Verapamil

Absorption:

About 90% of orally administered verapamil is absorbed. The mean bioavailability is as low as 22% because of extensive hepatic first-pass extraction, and shows great variation (10-35%). The mean bioavailability following repeated administration may increase to 30%. Food, especially fat food, may delay the absorption of verapamil from the tablet, which results in higherTmax-values and lower Cmax values, without influence on the bioavailability of verapamil. To prevent a potential delayed absorption it is recommended to take Tarka half an hour before breakfast.

Distribution and biotransformation:

The mean time to peak plasma concentration is 4 hours. The peak plasma concentration of nor-verapamil is attained about 6 hours post- dose. Steady state after multiple once daily dosing is reached after 3-4 days. Plasma protein binding of verapamil is about 90%.

Elimination:

The mean elimination half life after repeated administration is 8 hours. 3-4% of a dose is excreted renally as unchanged drug. Metabolite excretion is in the urine (70%) and in the feces (16%). Nor-verapamil is one of 12 metabolites identified in urine, has 10-20% of the pharmacologic activity of verapamil, and accounts for 6% of excreted drug. The steady- state plasma concentrations of nor-verapamil and verapamil are similar. Verapamil kinetics is not altered by renal function impairment. The bioavailability and elimination halflife of verapamil are increased in patients with liver cirrhosis. Verapamil kinetics is, however, unchanged in patients with compensated hepatic dysfunction. Kidney function has no effect on verapamil elimination.

Trandolapril

Absorption:

Orally administered trandolapril is absorbed rapidly Absorption is 40-60% and independent of the presence of food. The time to peak plasma concentration is about 30 minutes.

Distribution and biotransformation:

Trandolapril disappears very rapidly from plasma, and its half life is less than one hour. Trandolapril is hydrolyzed in plasma to form trandolaprilat, a specific angiotensin converting enzyme (ACE) inhibitor The amount of trandolaprilat formed is independent of food intake. The time to peak plasma concentration of trandolaprilat is 4-6 hours. Plasma protein binding of trandolaprilat is greater than 80%. Trandolaprilat binds with great affinity to ACE, and this is a saturable process. Most of circulating trandolaprilat binds to albumin in a non-saturable process. Steady state after multiple once daily dosing is reached after about 4 days in healthy volunteers as well as in younger and elderly hypertensive patients.The effective half-life calculated from accumulation is 16-24 hours.

Elimination:

10-15% of an administered trandolapril dose is excreted as unchanged trandolaprilat in urine. Following oral administration of radioactively labeled trandolapril, one third of radioactivity is recovered in urine and two thirds in feces. The renal clearance of trandolaprilat shows a linear correlation with creatinine clearance.The trandolaprilat plasma concentration is significantly higher in patients whose creatinine clearance is [≤] 30 ml/min. Following repeated administration to patients with chronic renal dysfunction, steady state is, however, also reached after four days, independently of the extent of kidney function impairment. The trandolapril plasma concentration may be 10 times higher in patients with liver cirrhosis than in healthy volunteers. The plasma concentration and renal excretion of trandolaprilat are also increased in cirrhotic patients, albeit to a lesser extent. Trandolapril(at) kinetics are unchanged in patients with compensated hepatic dysfunction.

Tarka

As there are no known kinetic interactions between verapamil and trandolapril or trandolaprilat, the single-active substance active substance kineticparameters of these two active substances apply to the combination product as well.

PHARMACEUTICAL PARTICULARS

Incompatibilities
Not applicable.

Shelf life
2 years

Special precautions for storage
Store in original pack. Do not store above 25ºC.

HOW SUPPLIED

Blister packs of 14, 28, 30, 50, 56, 98, 280 tablets.
Not all pack sizes may be marketed

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Abbott