TARKA® 240/4
(Verapamil/Trandolapril)

NAME OF THE MEDICINAL PRODUCT

Tarka240 mg / 4 mg modified-releasetablet

DESCRIPTION AND COMPOSITION

Tarka 240 mg / 4 mg tablet: ocher, oval, marked with Knoll logo and "244" on one face, film coated tablet containing 240 mg of verapamil hydrochloride and 4 mg of trandolapril in a modified-release presentation

CLINICAL PARTICULARS

Therapeutic indication

Tarka 240/4 mg modified-released tablets are indicated for the treatment of essential hypertension in patients whose blood pressure has been normalised on the individual components in the same proportion of doses.

Posology and method of administration

The usualdosage isone tabletoncedaily taken inthe morningat least ahalfan hour beforebreakfast and at approximately the same time each day. The tablets should be swallowed whole.

Individual dose titration with the components is recommended. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Children and adolescents: Tarka is contraindicated in children and adolescents (<18 years).

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.

Renal insufficiency: Tarka is contraindicated in severe renal impairment.

Hepatic insufficiency: the use of Tarka is not recommended in patients with severe hepatic impairment; Tarka is contraindicated in patients with liver cirrhosis with ascites.

Contraindications

Hypersensitivity to trandolapril or any other ACE inhibitor and/or verapamil or to any of the excipients, History of angioneurotic oedema associated with previous ACE inhibitor therapy Hereditary/idiopathic angioneurotic oedema, Cardiogenic shock, Recent myocardial infarction with complications, Second-or third-degree AV block without a functioning pacemaker, SA block, Sick sinus syndrome in patients without a functioning pacemaker, Congestive heart failure, Atrial flutter/fibrillation in association with an accessory pathway (e.g. WPW-syndrome), Severe renal impairment (creatinine clearance <30 ml/min), Dialysis, Liver cirrhosis with ascites. Aortic or mitral stenosis, obstructive hypertrophic cardiomyopathy, Primary aldosteronism. Second and third trimester of pregnancy, Use in children and adolescents (<18 years), Is contraindicated in patients concomitantly treated with i. v. β- adrenoreceptorantagonists (exception: intensivecare unit).

Special warnings and special 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, diarrhoea or vomiting; decreasedleft ventricular function, renovascular hypertension). Such patients should havetheir volume orsalt depletioncorrectedbeforehandand therapy shouldpreferablybe 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 canusuallybe continued oncebloodvolumeand pressure havebeen effectivelycorrected. Close monitoring during initiation of therapy and dose adjustment is also needed in patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

Kidney function impairment:

Patients with moderate renal impairment should have their kidney function monitored. Tarka may producehyperkalaemiain patients with renal dysfunction. Acute deterioration of kidney function (acute renal failure) may occur especially in patientswith pre-existing kidney function impairment, or congestive heart failure. There is insufficient 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 tosufferan acutelossof kidney function.

Proteinuria

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

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor

Severe hepatic impairment:

Since there is insufficient therapeutic experience in patients with severe hepatic impairment, the use of Tarka cannot be recommended. Tarka is contraindicated in patients with severe liver cirrhosis with ascites. Very rarely, ACE inhibitor therapy has been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and sometimes death. The mechanism of this syndrome is not understood. Patients receiving Tarka who develop jaundice or marked elevations of hepatic enzymes should discontinue Tarka and receive medical follow-up.

Angioneurotic oedema:

Rarely, ACE inhibitors (such as trandolapril) may cause angioneurotic oedema that includes swelling of the face, extremities, tongue, glottis, and/or larynx. Patients experiencing angioneurotic oedema must immediately discontinue trandolapril therapy and be monitored until oedema resolution. Angioneurotic oedema confined to the face will usually resolve spontaneously. Oedema 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 oedema 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 oedema, and Tarka is contraindicated if angioneurotic oedema wasan adverse reaction to an ACE inhibitor.

Neutropenia/agranulocytosis

The risk of neutropenia appears to be dose-and type-related and is dependent on the 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:

Hyperkalaemia 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 hasbeen studied in a limited number of elderly hypertensivepatients 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 anaesthesia, ACE inhibitors may produce hypotension, which can be correctedby plasmavolume expanders.

Conduction d isturbanc es:

Treatments should be used with caution in patients with first-degree atrioventricular block.

Bradycardia:

Tarkashould be usedwith caution in patients with bradycardia.

D seases in which neuromuscular transmissionis 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).

Desensitisation:

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

LDL-aphaeresis:

Life threatening anaphylactoid reactions havebeen noted when patients on LDL-aphaeresis 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. Bloodpressurereadingsfor evaluation of therapeutic response to Tarka should always be taken before the next dose.

Lactose:

Tarka240/4mg modified-release tabletscontain lactose. Eachmodified-release tabletcontains110.37 mgof lactosemonohydrate. Patientswithrare hereditaryproblemsof galactoseintolerance, the Lapp lactasedeficiencyor glucose-galactose malabsorption should nottake this medicinalproduct.

Sodium

This medicinal product contains 1.49 mmol (or 34.3 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

Lithium:

The combination of lithium and Tarka is not recommended.

Lactation:

The use of Tarka is not recommended in women whom are breastfeeding

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 hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.
- Dantrolene: The simultaneous use of verapamil with dantrolene is not recommended.

Precautions for use

- *Antihypertensive medicinal products:* increase of the hypotensive effect of Tarka.
- *Diuretics:* patients on diuretics and especially those who are 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. Furtherincreases in dosage should be performedwith 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 anaesthetics), 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 oedema 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 (such as neuromuscular blockers) may be enhanced.
- *Tranquilisers/antidepressants:* as with all antihypertensives, there is an elevated risk of orthostatic hypotension when combining Tarka with major tranquilisers or antidepressant medicinal products containing imipramine

Take into account

- *Non-steroidal anti-inflammatory drugs (NSAIDs):* the administration of a non-steroidal anti-inflammatory drugs may reduce the antihypertensive effect of an ACE inhibitor Furthermore it has been described that NSAIDs and ACE 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 compromisedrenal function.
- *Antacids:* induce decreased bioavailability of ACE inhibitors.
- *Sympathomimetics:* may reduce the antihypertensive effects of ACE inhibitors; patient should be carefully monitored to confirm thatthe desired effect is being obtained.
- *Alcohol:* enhances the hypotensiveeffect.
- *In vitro* metabolic studies indicate that verapamil is metabolised by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Verapamil is a known inhibitor of CYP3A4 enzymes. Clinically significant interactions have been reported with inhibitors of CYP3A4 causing elevation of plasma levels of verapamil, while inducers of CYP3A4 have caused lowering of plasma levels of verapamil, therefore patients should be monitored for drug interactions. Examplesof such interactionsare:

  Verapamil may increase the plasma concentrations of *carbamazepine, cyclosporin, and theophylline* thus increasing risk of toxicity from these compounds.
- *Rifampin, phenytoin, and phenobarbital* reduce the plasma concentrations of verapamil, whereas cimetidine may increase the plasma concentrations of verapamil.
- Verapamil may increase plasma concentrations of *prazosin*.
- *HMG-CoA Reductase Inhibitors:* An increase in serum exposure has been reported for simvastatin (metabolised by CYP3A4) when concomitantly administered with verapamil. The concomitant administration of verapamil and high doses of simvastatin has been reported to increase the risk of myopathia/rabdomyolsis. The dose of simvastatin (and other statins metabolised by CYP3A4 such as atorvastatin and lovastatin) should be adapted accordingly.
- *Antidiabetics:* a dose adjustment of antidiabetics or of Tarka may be necessary in individual cases especially at the startof therapy due to increased reduction of blood glucose.
- *Acetylsalicylic Acid (Aspirin):* The concomitant us of acetylsalicylic acid can increase the side effect profile of acetylsalicylic acid (mayincrease theriskof bleeding).
- *Grapefruit* juice has been shown to increase the plasma levels of verapamil, which is a component of Tarka. Grapefruit juice should therefore not be ingested with Tarka.

  It has been demonstrated that some foods can decrease the speed, but not the amount of the absorption of verapamil. It is therefore recommended that Tarka is taken at least half an hour before breakfast.

Pregnancy and Lactation

Pregnancy

Tarka should not be used during the first trimester of pregnancy When pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible Controlled studies with ACE inhibitors have not been done in humans, but limited number of cases with first trimester exposure have not appeared to manifest malformations consistent with human foetotoxicity as described below.

The use of Tarka is contraindicated during the second and third trimester of pregnancy Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia. Should exposure of Tarka have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended Infants whose mothers have taken Tarka should be closely monitored for hypotension, oliguria and hyperkalaemia. ACE inhibitors, which cross the placenta, have been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion. Verapamil may inhibit contractions if used at the end of the pregnancy. Also, foetal bradycardia and hypotension cannot be excluded, based on the pharmacologicalproperties. It is not known whether trandolapril is excreted into human breast milk

Verapamil is excreted in low amounts into human breast milk. The use of Tarka is not recommended in women who are breastfeeding

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. There are no data available, but an effectcannot be ruled out, since the undesirable effectssuch as dizziness and fatigue can occur.

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 adverse drug reactions are ranked under headings of frequency, using the following convention: common (>1/100, <1/10), uncommon (>1/1, 000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10, 000), including isolatedreports.

System Organ Class	Frequency	Undesirable Effects
Blood & lymphatic system disorders	very rare	leukopenia pancytopenia thrombocytopenia
Immune system disorders	uncommon veryrare	allergic reaction, unspecified increase in gammaglobulin hypersensitivity unspecified
Metabolism & nutritional disorders		hyperlipidaemia
Psychiatric disorders	uncommon veryrare	somnolence aggression anxiety depression
Nervous system disorders	 veryrare	dizziness vertigo tremor collapse impaired balance insomnia paresthesia or hyperesthesia, syncope or acute circulatory failures with loss of consciousness, tasteaberration, weakness
Eye disorders	very rare	abnormal/blurredvision
Cardiac disorders/ vascular disorders	uncommon veryrare	hot flushes AV block, firstdegree palpitation anginapectoris atrial fibrillation AV block, complete AV block, unspecified bradycardia cardiac arrest

		cerebralhemorrhage edema, peripheral edema, unspecified flushing heart failure hypotensiveevents including orthostasis or fluctuation of blood pressure tachycardia
Respiratory, thoracic & mediastinaldisorders	very rare	cough asthma, bronchitis, dyspnea sinus congestion
Gastrointestinal disorders	very rare	constipation abdominal pain diarrhea gastrointestinal disorders unspecified nausea dry mouth/throat pancreatitis vomiting
Hepatobiliarydisorders	very rare	cholestasis hepatitis increase in GT increase in LDH increase in lipase jaundice
Skin & subcutaneous tissue disorders	very rare	facialedema pruritus rash sweating increased alopecia herpes simplex skin disorders, unspecified angioneurotic edema erythemamultiforme exanthema or dermatitis psoriasis urticaria
Musculoskeletal, connectivetissue & bone disorders	very rare	arthralgia myalgia myasthenia
Renal and urinary disorders	very rare	polyuria acute renal failure
Reproductive system & breast disorders	very rare	gynecomastia impotence
General disorders & administration site conditions	very rare	headache chest pain fatigue or asthenia
Investigations	very rare	liver function test, abnormal hyperbilirubinemia increase in alkaline phosphatase increase in serum potassium increasein transaminases

The following adverse reactions have notyet been reported in relation to Tarka, but are generally accepted as being attributableto ACE inhibitors:

- *Blood and lymphatic system disorders:* decreases in haemoglobin and haematocrit, and in individual cases agranulocytosis. Isolated cases of haemolytic anaemia have been reported in patients with congenital G-6-PDH deficiency
- *Psychiatric disorders:* occasionallyconfusion.
- *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 ischemic attacks have been reported for ACE inhibitors in association with hypotension.
- *Respiratory, thoracic and mediastinal disorders:* Rarely, sinusitis, rhinitis, glossitis, and bronchospasm.
- *Gastrointestinal disorders:* occasionallyindigestion. Individual cases of ileus.
- *Hepatobiliary disorders:* individual cases of cholestatic icterus.
- *Skin and subcutaneous tissue disorders:* occasionally allergic and hypersensitivity reactions such as Stevens-Johnson syndrome, toxic epidermal 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 the presence of renal insufficiency, severe heart failure and renovascular hypertension. These increases are however reversible on discontinuation.

Symptomatic or severe hypotension has occasionally occurred after initiation of therapy with ACE inhibitors. This occurs especially in certain risk groups, such as patients with a stimulated renin-angiotensin-aldosteronesystem.

The following adverse reactions have notyet been reported in relation to Tarka, but are generally acceptedas being attributable to phenylalkylamine calcium-channel blockers

- *Nervous system disorders:* in some cases, there may be extrapyramidal symptoms (Parkinson's disease, choreoathetosis, dystonic syndrome). Experience so far has shown that these symptoms resolve once the medicinal product is discontinued. There have been isolated reports of exacerbationof myasthenia gravis, Lambert-Eaton syndromeand advancedcases of Duchenne's muscular dystrophy
- *Gastrointestinal disorders:* gingival hyperplasia following long-term treatment is extremely rare and reversibleafter discontinuation of therapy.
- *Skin and subcutaneous tissue disorders:* Stevens-Johnson syndrome and erythromelalgia have beendescribed. In isolatedcases allergicskin reactionslike 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

The highest dose used in clinical trials was 16 mg of trandolapril. This dose produced no signs or symptoms of intolerance. During overdose with Tarka, the following signs and symptoms may occur due to the verapamil component: hypotension, bradycardia, AV block, asytole and negative inotropy. Fatalities have occurred as a result of overdose.

During overdose with Tarka, the following signs and symptoms may occur due to the ACE inhibitor component: severehypotension, shock, stupor bradycardia, electrolyte disturbance, renal failure, hyperventilation, tachycardia, palpitations, dizziness, anxiety, and cough.

Treatment:

After ingestion of an overdose of Tarka Tablets total intestinal lavageshouldbe considered. Further absorption of verapamil present in the gastrointestinal tract should be prevented by gastric lavage, administration of an absorbent (activated charcoal)and a laxative.

Except for general measures (maintenance of an adequate circulation volume with plasma or plasma replacements) against severe hypotension (e.g. shock), inotropic support with dopamine dobutamine or isoprenaline canalsobe administered.

Treatment of overdose with Tarka should be supportive. Treatment of the overdose of the verapamil hydrochloride component has included the administration of parenteralcalcium, beta adrenergic stimulation and gastrointestinal irrigation. Due to the potential for delayed absorption of the sustained release verapamil portion of Tarka, patients may require observation and hospitalisation for up to 48 hours. Verapamil hydrochloride can not be removed by haemodialysis.

The recommended treatment of trandolapril overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures to eliminate trandolapril (e.g. emesis, gastric lavage, administration of absorbents and sodium sulphate). It is not known whether trandolapril (orthe active metabolite, trandolaprilat) can be removed via haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Tarka is a fixed combination of the heart-rate lowering calcium antagonist verapamil and the ACE inhibitortrandolapril.

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 inthe heart.

The mechanism of action of verapamil produces the following effects:

1. Arterial vasodilation. In general, verapamil reduces arterial pressure both at rest and at a given levelofexercise by dilatingperipheral arterioles. This reduction in peripheral resistance (afterload) reducesmyocardialoxygen requirements & energyconsumption
2. Reduction of myocardial contractility. The negative inotropic activity of verapamil can be compensated by the reduction in peripheral resistance.

   The cardiac index will not be decreased unless in patients with pre-existing left ventricular dys-function. 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, arenot 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 latter 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 onthe renin secretionresults in an increase ofthe plasmarenin 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 andlocal kallikrein-kininsystemwhichcontributestoperipheralvasodilation byactivating the prostaglandinsystem. It is possible thatthis mechanism is involved inthe 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 resistanceis reduced with either nochange or an increase in cardiacoutput.

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 therapyhas notbeen associated with a rapid increase in blood pressure. Theantihypertensive effectof trandolapril setsin one hour post-dose andlasts foratleast24 hours, buttrandolaprildoes notinterferewiththe circadian bloodpressure pattern.

Tarka

Neither animal studies nor healthy volunteer studies could demonstrate pharmacokinetic or RAS inter actions between verapamil and trandolapril. The observed synergistic activity of these two active substances must therefore be due to their complementary pharmacodynamic actions. In clinicaltrials Tarka wasmore effective in reducinghigh blood pressure thaneitheractivesubstance alone.

Pharmacokinetic properties

Tarka tablets are film-coated and composed of a layer designed for sustained release of verapamil hydrochloride and a separate layerintendedfor immediaterelease 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 fatty food, may delay the absorption of verapamil from the tablet, which results in higher t_{max}-values and lower C_{max} and AUC_{0-24} values. To prevent a potential delayed absorption it is recommended to take Tarka Tablets at leasthalf an hour beforebreakfast.

Distribution and biotransformation

The mean time to peak plasma concentration is 4 hours. The peak plasma concentration of norverapamil is attained about 6 hours post-dose. Steady state after multiple oncedailydosingis 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 faeces (16%). Norverapamil 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 norverapamil and verapamil are similar. Verapamil kinetics is not altered by renal function impair ment. The bioavailability and elimination half life 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 disappearsvery rapidly fromplasma, andits half life is lessthanone hour.

Trandolapril is hydrolysed 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-saturableprocess. Steady stateafter multiple oncedaily dosing is reachedafter about 4 days in healthy volunteers aswellasin younger andelderly hypertensivepatients. The effectivehalf-life calculated from accumulationis 16-24hours.

Elimination:

10-15% of an administered trandolapril dose is excreted as unchanged trandolaprilat in urine. Following oral administration of radioactively labelled trandolapril, one third of radioactivity is recovered in urine and two thirds in faeces. The renal clearance of trandolaprilat shows a linear correlation withcreatinineclearance. The trandolaprilat plasma concentration is significantlyhigher in patients whose creatinine clearance is ≤ 30 ml/min. Following repeated administration to patients withchronicrenal dysfunction, steady state is, however, also reachedafterfour 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 andrenalexcretionof trandolaprilat arealso increased in cirrhotic patients, albeit to a lesserextent. Trandolapril (at) kineticsare unchanged in patientswith compensatedhepatic dysfunction.

Tarka

As there are no known kinetic interactions between verapamil and trandolapril or trandolaprilat, the singleactivesubstancekinetic parameters ofthesetwo activesubstances applytothe combination product as well.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable.

Special precautions for storage

Donot storeabove25°C.

HOW SUPPLIED

Blister packs of 14, 28, 30, 50, 56, 98, 280modified-releasetablets

Not all pack sizes may be marketed.

Date of revision of the text

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Abbott