Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tarka 180 mg/2 mg modified-release tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient: 107 mg lactose monohydrate/modified-release tablet.

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet.
Pink, oval, marked with the Knoll logo and “182” on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Refer to section 4.4 (Special warnings and precautions for use).

4.2 Posology and method of administration

The usual dosage is one tablet once daily, taken in the morning before, with or after breakfast. The tablets should be swallowed whole.

Children and adolescents: Tarka is contraindicated in children and adolescents (<18 years) (see also section 4.3).

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 section 4.4).

Renal insufficiency: Tarka is contraindicated in severe renal impairment (see section 4.3).

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 (see sections 4.3 and 4.4).

4.3 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
- 2^{nd} and 3^{rd} trimester of pregnancy (see sections 4.4 and 4.6)
- Use in children and adolescents (< 18 years)
- Is contraindicated in patients concomitantly treated with i.v. β-adrenoreceptor antagonists (exception: intensive care unit)

4.4 Special warnings and precautions for use

Symptomatic hypotension:
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; decreased left ventricular function, renovascular hypertension).

Such patients should have their volume or salt depletion corrected beforehand 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.

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 (see also section 4.3):
Patients with moderate renal impairment should have their kidney function monitored.

Tarka may produce hyperkalaemia in patients with renal dysfunction.

Acute deterioration of kidney function (acute renal failure) may occur especially in patients with 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 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.

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 (see section 4.5).

Severe hepatic impairment:
Since there is insufficient therapeutic experience in patients with severe hepatic impairment as such, the use of Tarka cannot be recommended. Tarka is contraindicated in patients with liver cirrhosis with ascites (see also section 4.3). 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 was an adverse reaction to an ACE inhibitor (see also section 4.3).

Intestinal angioedema:
Intestinal angioedema has also been reported in patients treated with ACE inhibitors. This should be considered in patients on Tarka presenting with abdominal pain (with or without nausea or vomiting).

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 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 anaesthesia, ACE inhibitors may produce hypotension, which can be corrected by plasma volume expanders.

Conduction disturbances:
Treatments should be used with caution in patients with first degree atrioventricular block (see also section 4.3).

Bradycardia:
Tarka should be used with caution in patients with bradycardia (see also section 4.3).

Diseases in which neuromuscular transmission 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).

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 have been 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.

Blood pressure readings for evaluation of therapeutic response to Tarka should always be taken before the next dose.

Lactose:
Tarka 180/2 mg modified release tablets contain lactose. Each modified-release tablet contains 107 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium:
This medicinal product contains 1.12 mmol (or 25.77 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 (see section 4.5).

Pregnancy:
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Lactation:
The use of Tarka is not recommended in women whom are breastfeeding (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with other medicinal products may occur as a result of a pharmacodynamic or pharmacokinetic interaction or a combination of both. In cases where events are associated with both pharmacodynamic and pharmacokinetic interactions a cross reference to the relevant section is included.

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.

- 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 (see section 4.4).

- Intravenous beta-blockers should not be administered during treatment with Tarka (see section 4.3). The combination of verapamil with beta-blockers may provide a strong AV-conduction disturbance, which in some cases may lead to severe bradycardia: serious cardiodepression may also arise.

- Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (P-gp). Verapamil is known to inhibit CYP3A and P-gp. When verapamil and colchicine are administered together, inhibition of P-gp and/or CYP3A by verapamil may lead to increased exposure to colchicine. Combined use is not recommended.

Precautions for use

- *Antihypertensive medicinal products*: increase of the hypotensive effect of Tarka (see Pharmacokinetic Interactions with Verapamil).

- *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. Further increases in dosage should be performed with caution.

- *Anaesthetics*: Tarka may enhance the hypotensive effects of certain anaesthetic medicinal products.

- *Narcotics/antipsychotics*: postural hypotension may occur.

- *Tranquillisers/antidepressants*: as with all antihypertensives, there is an elevated risk of orthostatic hypotension when combining Tarka with major tranquillisers or antidepressant medicinal products containing imipramine (see Pharmacokinetic Interactions with Verapamil).

- *Allopurinol, cytostatic or immunosuppressive medicinal products, systemic corticosteroids or procainamide*: concomitant administration with ACE inhibitors may lead to an increased risk for leukopenia (see Pharmacokinetic Interactions with Verapamil).

- *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 (see Pharmacokinetic Interactions with Verapamil).

- *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 (see Pharmacokinetic Interactions with Verapamil).

- *Digoxin and Digitoxin*: concurrent use of digoxin and verapamil has been reported to result in 50-75% higher digoxin plasma concentrations, requiring reduction of the digoxin and digitoxin dosage. Verapamil has also been shown to reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29% respectively (see Pharmacokinetic Interactions with Verapamil).

- *Muscle relaxants*: the effect of muscle relaxants (such as neuromuscular blockers) may be enhanced.

Take into account

- *Non-steroidal anti-inflammatory drugs (NSAIDs)*: the administration of 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 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 of Tarka.

- *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 (see section 4.4).

- *Acetylsalicylic Acid (Aspirin)*: The concomitant us of acetylsalicylic acid can increase the side effect profile of acetylsalicylic acid (may increase the risk of bleeding).

Pharmacokinetic Interactions with Verapamil:
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 and P-gp. 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. Examples of such interactions are:

(a) Verapamil may increase the plasma concentrations of:

- *almotriptan, buspirone, carbamazepine, ciclosporin, digoxin, digitoxin, doxorubicin, everolimus, glyburide (glibenclamide), imipramine, metoprolol, midazolam, prazosin, propranolol, quinidine, sirolimus, tacrolimus, terazosin* and *theophylline* thus increasing risk of toxicity from these compounds. Where appropriate, dose adjustment or additional monitoring of plasma concentrations should be considered

- *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/rhabdomyolysis. The dose of simvastatin (and other statins metabolised by CYP3A4 such as atorvastatin and lovastatin) should be adapted accordingly.

(b) Verapamil concentrations may be increased by:

- *atorvastatin, cimetidine, clarithromycin, erythromycin* and *telithromycin.*
- *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.

(c) Verapamil concentrations may be reduced by:

- *phenobarbital, phenytoin, rifampicin, sulfipyrazone* and *St. John's Wort.*

4.6 Fertility, pregnancy and lactation

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).

Pregnancy
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor therapy 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) (see section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Verapamil may inhibit contractions if used at the end of the pregnancy. Also, foetal bradycardia and hypotension cannot be excluded, based on the pharmacological properties.

Lactation
Verapamil is excreted in low amounts into human breast milk. There is no information available regarding the use of trandolapril during breastfeeding.

Tarka is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 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 effect cannot be ruled out, since the undesirable effects such as dizziness and fatigue can occur.

4.8 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 flush (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: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**Undesirable Effects**
Infections and infestations		
	rare	- herpes simplex
	very rare	- bronchitis
Blood and lymphatic system disorders		
	very rare	- leukopenia
		- pancytopenia
		- thrombocytopenia
Immune system disorders		
	uncommon	- hypersensitivity

Metabolism and nutrition disorders		
	uncommon	- hyperlipidaemia
	rare	- anorexia
Psychiatric disorders		
	very rare	- aggression
		- anxiety
		- depression
		- nervousness
Nervous system disorders		
	common	- dizziness
		- headache
	uncommon	- tremor
		- somnolence
	rare	- syncope
	very rare	- balance disorder
		- insomnia
		- paraesthesia
		- hyperaesthesia
		- loss of consciousness
		- dysgeusia
		- cerebral haemorrhage
Eye disorders		
	very rare	- visual impairment
		- vision blurred
Ear and labyrinth disorders		
	common	- vertigo
Cardiac disorders		
	uncommon	- atrioventricular block first degree
		- palpitations
	very rare	- angina pectoris
		- atrial fibrillation
		- atrioventricular block complete
		- atrioventricular block
		- bradycardia
		- cardiac arrest
		- cardiac failure
		- tachycardia
Vascular disorders		
	common	- hot flush
	very rare	- shock
		- flushing
		- hypotension (see also section 4.4)
		- orthostatic hypotension (see also section 4.4)
		- blood pressure fluctuation (see also section 4.4)
Respiratory, thoracic and mediastinal disorders		
	common	- cough
	very rare	- asthma
		- dyspnoea

	-	sinus congestion
Gastrointestinal disorders		
common	-	constipation
uncommon	-	abdominal pain
	-	diarrhoea
	-	gastrointestinal disorder
	-	nausea
very rare	-	dry mouth
	-	dry throat
	-	pancreatitis
	-	vomiting
Hepatobiliary disorders		
rare	-	hyperbilirubinaemia
very rare	-	cholestasis
	-	hepatitis
	-	jaundice
Skin and subcutaneous tissue disorders		
uncommon	-	face oedema
	-	pruritus
	-	rash
	-	hyperhidrosis
rare	-	alopecia
	-	skin disorder
very rare	-	angioedema (see also section 4.4)
	-	erythema multiforme
	-	dermatitis
	-	psoriasis
	-	urticaria
not known	-	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders		
very rare	-	arthralgia
	-	myalgia
	-	muscular weakness
Renal and urinary disorders		
uncommon	-	polyuria
very rare	-	renal failure acute (see also section 4.4)
Reproductive system and breast disorders		
very rare	-	gynaecomastia
	-	erectile dysfunction
General disorders and administration site conditions		
uncommon	-	chest pain
very rare	-	fatigue
	-	asthenia
	-	oedema peripheral
	-	oedema
Investigations		
uncommon	-	liver function test abnormal
very rare	-	blood alkaline phosphatase increased
	-	blood potassium increased
	-	transaminases increased

- immunoglobulins increased
- gamma-glutamyltransferase increased
- blood lactate dehydrogenase increased
- lipase increased

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

- *Infections and infestations*: Rarely, sinusitis and rhinitis.
- *Blood and lymphatic system disorders*: Haemoglobin decreased, haematocrit decreased and individual cases agranulocytosis. Isolated cases of haemolytic anaemia have been reported in patients with glucose-6-phosphate dehydrogenase deficiency.
- *Psychiatric disorders*: Occasionally confusional state and rarely sleep disorder.
- *Nervous system disorders*: Rarely, balance disorder and transient ischaemic attack.
- *Ear and labyrinth disorders*: Tinnitus.
- *Cardiac disorders*: Individual cases of arrhythmia and myocardial infarction have been reported for ACE inhibitors in association with hypotension.
- *Respiratory, thoracic and mediastinal disorders*: Rarely, bronchospasm.
- *Gastrointestinal disorders*: Intestinal angioedema. Occasionally dyspepsia, individual cases of ileus and glossitis.
- *Hepatobiliary disorders*: Individual cases of cholestatic jaundice.
- *Skin and subcutaneous tissue disorders*: Occasionally hypersensitivity such as toxic epidermal necrolysis. This can be accompanied by pyrexia, myalgia, arthralgia, eosinophilia and / or antinuclear antibody increased.
- *Investigations*: Blood urea increased and blood creatinine increased may occur especially in the presence of renal failure, cardiac 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-aldosterone system.

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

- *Endocrine disorders*: Hyperprolactinaemia has been described.
- *Nervous system disorders*: In some cases, there may be extrapyramidal disorder (such as Parkinson's disease, choreoathetosis, dystonia). Experience so far has shown that these symptoms resolve once the medicinal product is discontinued. There have been isolated reports of myasthenia gravis, myasthenic syndrome (such as Lambert-Eaton syndrome) and advanced cases of Duchenne muscular dystrophy. There has been a single postmarketing report of paralysis (tetraparesis) associated with the combined use of verapamil and colchicine. This may have been caused by colchicine crossing the blood brain barrier due to CYP3A4 and P-gp inhibition by verapamil. Combined use of verapamil and colchicine is not recommended (see also section 4.5).
- *Gastrointestinal disorders*: Gingival hyperplasia following long-term treatment is extremely rare and reversible after discontinuation of therapy.
- *Skin and subcutaneous tissue disorders*: Erythromelalgia has been described. In isolated cases allergic dermatitis, such as erythema.
- *Reproductive system and breast disorders*: Galactorrhoea has been described.

Hypotension in patients with angina pectoris or cerebrovascular disorder treated with verapamil may result in myocardial infarction or cerebrovascular accident.

4.9 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, asystole 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: severe hypotension, 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 lavage should be 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 can also be administered.

Treatment of overdose with Tarka should be supportive. Treatment of the overdose of the verapamil hydrochloride component has included the administration of parenteral calcium, 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 (or the 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Trandolapril and Verapamil
ATC code: C09BB10

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

<u>Verapamil</u>
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.

In general, 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 pre-existing 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 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 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 therapy has not been associated with a rapid increase in blood pressure.

The antihypertensive 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.

5.2 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%.

The presence of food has no significant effect on the bioavailability of verapamil and norverapamil.

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 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 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 impairment.

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 disappears very rapidly from plasma, and its half-life is less than one 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 nonsaturable 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 labelled trandolapril, one third of radioactivity is recovered in urine and two thirds in faeces.

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 kinetic parameters of these two active substances apply to the combination product as well.

5.3 Preclinical safety data

General toxicity effects were observed in animals only at exposures that were sufficiently in excess of the maximum human exposure to make any concern for human safety negligible. Genotoxicity assays revealed no special hazard for humans.

Animal studies have shown that ACE inhibitors tend to have an adverse effect on late foetal development, resulting in foetal death and congenital abnormalities of the skull in particular. Foetoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These abnormalities are thought to be partly due to the pharmacologic activity of these active substances and may be related to ACE inhibitor-induced oligohydramnios. The abnormalities may also be partly due to ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.

There is no evidence of tumorigenic potential with either trandolapril or verapamil.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ingredients of tablet core
verapamil granule:

Microcrystalline cellulose
Sodium alginate
Povidone
Magnesium stearate

trandolapril granule:

Maize starch
Lactose monohydrate
Povidone
Hypromellose
Sodium stearyl fumarate

Ingredients of the tablet coating
Hypromellose
Hyprolose
Marcrogol 400
Marcrogol 6000
Talc
Silica, colloidal anhydrous
Docusate sodium
Titanium dioxide, E171
Iron oxide, red E172
Iron oxide, yellow E172
Iron oxide, black E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

Transparent, colourless PVC/PVDC-aluminium blister packaging.
Box of 14, 28, 30, 50, 56, 98, 280 modified-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ireland Limited
4051 Kingswood Drive
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 0038/089/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2005
Renewal of authorisation: 16 March 2010

10 DATE OF REVISION OF THE TEXT

December 2012