AUSTRALIAN PRODUCT INFORMATION

TARKA® 2/180
TARKA® 4/240

(trandolapril/verapamil hydrochloride) film coated tablet

1 NAME OF THE MEDICINE

Trandolapril/verapamil hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TARKA 2/180 contains trandolapril 2 mg and verapamil 180 mg modified release as the active ingredients in pink, oval, film coated tablets. TARKA 2/180 also contain 107.00 mg lactose monohydrate.

TARKA 4/240 contains trandolapril 4 mg and verapamil 240 mg modified release as the active ingredients in red-brown, oval, film coated tablets. TARKA 4/240 also contain 110.37 mg lactose monohydrate.

Excipients with known effect: Contains sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

TARKA 2/180 are pink, oval, film coated tablets embossed with '182' on one face.

TARKA 4/240 are red-brown, oval, film coated tablets embossed with '244' on one face.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TARKA is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed dose combination.

4.2 DOSE AND METHOD OF ADMINISTRATION

The product should be swallowed whole with water ideally in the morning with or after food.

Adults

The usual dosage is one tablet daily. The maximum dose of TARKA is 4/240 mg once daily.

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.

Children

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

Angina

The safety and efficacy of TARKA has not been evaluated in the treatment of angina.

4.3 CONTRAINDICATIONS

TARKA is contraindicated in:

- Patients who are hypersensitive to trandolapril or any other ACE inhibitor or to verapamil hydrochloride or to any of the inactive ingredients;

- Use in children and adolescents (<18 years)

- Patients concomitantly treated with intravenous β-adrenoreceptor antagonists (exception: intensive care unit, see Section 4.5 Interactions with other medicines and other forms of interactions).

Because of the trandolapril component, TARKA is contraindicated in:

- Pregnancy (see Section 4.4 Special warnings and precautions for use and Section 4.6 Fertility, Pregnancy and Lactation – Use in Pregnancy);

- Lactation (see Section 4.6 Fertility, Pregnancy and Lactation – Use in lactation);

- Severe renal impairment (creatinine clearance <30 mL/min)

- Dialysis

- Concomitant use with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m2) (see Section 4.4 Special warnings and precautions for use and Section 4.5 Interactions with other medicines and other forms of interactions).

- Liver cirrhosis with ascites

- Patients with a history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an angiotensin converting enzyme inhibitor;

- Hereditary/idiopathic angioedema

- Concomitant use with neprilysin (neutral endopeptidase, NEP) inhibitors such as sacubitril and racecadotril (see Section 4.4 Special warnings and precautions for use and Section 4.5 Interactions with other medicines and other forms of interactions).

- Haemodialysis and other extracorporeal treatments. Patients haemodialysed using high-flux polyacrylonitrile (‘AN69’) membranes or patients undergoing low-density lipoprotein apheresis with dextran sulfate are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes (e.g. cuprophane or polysulphone PSF) for haemodialysis.

Because of the verapamil hydrochloride component, TARKA is contraindicated in:

- Severe left ventricular dysfunction (see Section 4.4 Special warnings and precautions for use).

- Hypotension (less than 90 mmHg systolic pressure) or cardiogenic shock.

- Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker).

- Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker).

- Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes) (see Section 4.4 Special warnings and precautions for use). These patients are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if verapamil hydrochloride is administered.

- Heart failure with reduced ejection fraction of less than 35%, and/or pulmonary wedge pressure above 20 mmHg.

- Patients concomitantly administered ivabradine (see Section 4.5 Interactions with other medicines and other forms of interactions).

- Simultaneous initiation of treatment with dabigatran etexilate and oral verapamil (see Section 4.5 Interactions with other medicines and other forms of interactions).

- Treatment initiation with oral verapamil in patients following major orthopaedic surgery who are already treated with dabigatran etexilate (see Section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Combination Product (TARKA)

TARKA is a combination of verapamil and trandolapril. Adverse events may result from either component of this medicine (see Section 4.4 Special warnings and precautions for use – Trandolapril Component and Section 4.4 Special warnings and precautions for use – Verapamil Component).

Renal Impairment

The combination product TARKA has not been evaluated in patients with impaired renal function, however information on the individual components is provided (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties – Trandolapril Component and Section 5.2 Pharmacokinetic properties – Verapamil Component).

Hepatic Impairment

The combination product TARKA has not been evaluated in patients with impaired hepatic function however information on the individual components is provided (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties – Trandolapril Component and Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties – Verapamil Component).

Lactose

TARKA contains lactose monohydrate, therefore patients with rare hereditary forms of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption syndrome should not take this medicine.

Trandolapril Component:

Angioedema

Severe life-threatening angioedema has been reported with most of the ACE inhibitors. The overall incidence is approximately 0.1% to 0.2%. There seems to be no sex difference in the incidence of angioedema or in the predisposition to angioedema in patients with heart failure or hypertension. ACE inhibitors have been shown to cause a higher rate of angioedema in black patients than in non-black patients. In the majority of reported cases, the symptoms occurred during the first week of therapy. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Usually the angioedema involves non-pitting oedema of the skin and oedema of the subcutaneous tissues and mucous membranes.

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors. In such cases, the product should be discontinued promptly and the patient observed carefully until the swelling disappears. In instances when swelling has been confined to the face and lips, the angioedema has generally resolved either without treatment or with antihistamines. Angioedema associated with laryngeal oedema is potentially life-threatening. Angioedema involving the tongue, glottis or larynx requires immediate subcutaneous administration of 0.3 – 0.5 mL of adrenaline (epinephrine) solution (1:1000) along with other therapeutic measures as appropriate.

Where involvement of the tongue, glottis, or larynx is likely to cause airway obstruction, appropriate therapy, including adrenaline (epinephrine) and oxygen administration, should be carried out promptly or the patient hospitalised. Failing a rapid response, oral/nasal intubation or securing an airway by surgical means (e.g. cricothyrotomy or tracheostomy) may be necessary, followed by mechanical ventilation. Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon.

Angioedema may occur with or without urticaria. The onset of angioedema associated with use of ACE inhibitors may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom-free intervals.

There are case reports where changing the patient over to another ACE inhibitor was followed by a recurrence of angioedema and others where it was not. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angioedema to a drug of this class (see Section 4.3 Contraindications).

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

Patients receiving coadministration of an ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitors (e.g. temsirolimus, sirolimus, everolimus) or vildagliptin may be at increased risk for angioedema.

As the concomitant inhibition of ACE and neprilysin (neutral endopeptidase, NEP) may increase the risk of angioedema, co-administration of ACE inhibitors and NEP inhibitors (e.g. sacubitril and racecadotril) is contraindicated (see Section 4.3 Contraindications and Section 4.5 Interactions with other medicines and other forms of interactions). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of trandolapril therapy. If treatment with sacubitril/valsartan is stopped, trandolapril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see Section 4.3 Contraindications and Section 4.5 Interactions with other medicines and other forms of interactions).

Patients experiencing angioneurotic oedema must immediately discontinue treatment and be monitored until the oedema resolves.

Anaphylactoid reactions during desensitisation

Life-threatening anaphylactoid reactions have occurred in patients receiving ACE inhibitors during desensitisation (e.g. to hymenoptera venom). These reactions were avoided when ACE inhibitors were temporarily withdrawn, but recurred on inadvertent rechallenge.

Hypotension

Hypotension may occur in patients commencing treatment with ACE inhibitors. Excessive hypotension is rarely seen in patients with uncomplicated hypertension but can develop in patients with impaired renal function, in those that are salt/volume depleted because of renovascular disease, diuretic therapy, vomiting or diarrhoea and in patients undergoing dialysis [see Section 4.4 Special warnings and precautions for use, Section 4.5 Interactions with other medicines and other forms of interactions and Section 4.8 Adverse effects (undesirable effects)]. In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed. This may be associated with syncope, neurological deficits, oliguria and/or progressive azotaemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started at low doses under very close supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased, or diuretic therapy is commenced or increased.

Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident, respectively. In all high-risk patients, it is advisable to initiate treatment at lower dosages than those usually recommended for uncomplicated patients.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased.

Hypotension Post Myocardial Infarction

If hypotension is present, after MI, it is recommended that the patient be closely monitored for at least six hours following the initial dose. Therapy should be initiated after hyponatraemia and/or hypovolaemia (if present) is corrected.

Use in Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors may be associated with oliguria and/or progressive azotaemia and rarely with acute renal failure and/or death.

In clinical studies with ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases are usually reversible upon discontinuation of treatment. ACE inhibitors should be avoided in patients with known or suspected renal artery stenosis. When an ACE inhibitor is given to a patient with stenosis of the renal artery supplying a solitary kidney or with bilateral renal artery stenosis, acute renal insufficiency may occur. ACE inhibition may also cause a decrease in renal function in patients with stenosis of the artery supplying a transplanted kidney. It is believed that renal artery stenosis reduces the pressure in the afferent glomerular arteriole, and transglomerular hydrostatic pressure is then maintained by angiotensin II-induced constriction of the efferent arteriole. When an ACE inhibitor is given, the efferent arteriole relaxes, glomerular filtration pressure falls, and renal failure may result. The thrombotic occlusion of a stenosed renal artery can be precipitated by ACE inhibitors.

Some hypertensive patients with no apparent pre-existing renovascular disease have developed increases in blood urea nitrogen and serum creatinine which is usually minor and transient. This is more likely to occur in patients with pre-existing renal impairment or in those on diuretics. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. If deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients, usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as deterioration of function may not be apparent from measurement of blood urea and serum creatinine.

Some ACE inhibitors including trandolapril have been associated with the occurrence of proteinuria (up to 0.7%) and/or decline in renal function in patients with one or more of the following characteristics: old age, pre-existing renal disease, concomitant treatment with potassium sparing diuretics or high doses of other diuretics, limited cardiac-reserve, or treatment with a non-steroidal anti-inflammatory drug.

Proteinuria

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

Combination with Angiotensin II receptor blockers or Aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see Section 4.3 Contraindications and Section 4.5 Interactions with other medicines and other forms of interactions).

Use in Hepatic Impairment

As trandolapril is a pro-drug metabolised in the liver to its active moiety, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound and, therefore, the formation of the bioactive metabolite trandolaprilat may be diminished, resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of the esterases in the liver).

Cough

A persistent dry (non-productive) irritating cough has been reported with most of the ACE inhibitors. The frequency of reports has been increasing since cough was first recognised as a side-effect of ACE inhibitor therapy. In various studies, the incidence of cough varies between 2% to 15% depending upon the drug, dosage and duration of use.

The cough is often worse when lying down or at night, and has been reported more frequently in women (who account for 2/3 of the reported cases). Patients who cough may have increased bronchial reactivity compared with those who do not. The observed higher frequency of this side-effect in non-smokers may be due to a higher level of tolerance of smokers to cough.

The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins that accumulate because of ACE inhibition. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drugs may be required in severe cases.

Hyperkalaemia

Because the ACE inhibitors decrease the formation of Angiotensin II and the subsequent production of aldosterone, serum potassium concentrations exceeding 5.5 mEq/L may occur. Hyperkalaemia is more likely in patients with some degree of renal impairment, those treated with potassium-sparing diuretics or potassium supplements, in those consuming potassium-containing salt substitutes and in those patients taking other active substances associated with increases in serum potassium (e.g. co-trimoxazole also known as trimethoprim/sulfamethoxazole) concomitantly. Diabetics, and particularly elderly diabetics and/or those having left ventricular dysfunction after myocardial infarction, may be at increased risk of hyperkalaemia. In some patients, hyponatraemia may coexist with hyperkalaemia. It is recommended that patients taking an ACE inhibitor should have serum electrolytes (including potassium, sodium & urea) measured from time to time. This is more important in patients taking diuretics.

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression (including leukopenia/neutropenia) have been reported with ACE inhibitors. The risk of neutropenia appears to be dose-and-type-related and is dependent in the patient's clinical status. These have mostly occurred in patients with pre-existing impaired renal function, connective tissue diseases such as collagen vascular disease, immunosuppressant therapy or a combination of these complicating factors. Most episodes of leukopenia and neutropenia have been single, transient occurrences without any associated clinical symptoms. In addition, data to establish a causal relationship are currently lacking.

It is recommended that periodic monitoring of white blood cell counts should be considered in patients with collagen vascular disease, renal disease (serum creatinine □ 180 µmol/L) and those on multiple drug therapy with agents known to be nephrotoxic or myelosuppressive.

Dermatological reactions

Dermatological reactions characterised by maculo-papular pruritic rashes and sometimes photosensitivity have been reported rarely with ACE inhibitors. Rare and occasionally severe skin reactions (e.g. lichenoid eruptions, psoriasis, pemphigus-like rash, rosacea, Stevens-Johnson syndrome) have also been reported. A causal relationship is sometimes difficult to assess.

Patients who develop a cutaneous reaction with one ACE inhibitor might not when switched to another drug of the same class, but there are reports of cross-reactivity.

Taste disturbances (Dysgeusia)

The incidence of taste disturbance was reported to be high (up to 12.5%) with high doses of one ACE inhibitor, but the overall incidence for the class is probably low (< 0.5%). However, the relevant data are scarce and difficult to interpret.

The taste disturbance has been described as a suppression of taste or a metallic sensation in the mouth. The dysgeusia usually occurs in the first few weeks of treatment and may disappear within 1 - 3 months despite continued treatment.

Surgery/anaesthesia

In patients undergoing major surgery or who require anaesthesia, hypotension due to anaesthetic agents may be greater in patients receiving ACE inhibitors because of interference with compensatory mechanisms associated with the renin-angiotensin system. If perioperative hypotension occurs, volume expansion would be required.

Dialysis

It is not known for certain if trandolapril or trandolaprilat are removed by dialysis. However, it would be expected that dialysis could remove the active moiety, trandolaprilat, from the circulation, resulting in a possible loss of control of blood pressure. Therefore, careful monitoring of the patient's blood pressure during dialysis is required and the dosage of trandolapril adjusted if needed.

Valvular stenosis

Trandolapril should not be used in patients with aortic stenosis or outflow obstructions. There has been some concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators, including ACE inhibitors. Vasodilators may tend to drop diastolic pressure, and hence coronary perfusion pressure, without producing the concomitant reduction in myocardial oxygen demand that normally accompanies vasodilatation. The true clinical importance of this concern is uncertain.

LDL Apheresis

Life threatening anaphylactoid reactions have been noted when patients on LDL-apheresis take ACE inhibitors at the same time.

Verapamil Component:

Heart failure

Verapamil has a negative inotropic effect which, in most patients, is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. In clinical experience with 4,954 patients, 87 (1.8%) developed congestive heart failure or pulmonary oedema. Verapamil should be avoided in patients with severe left ventricular dysfunction (e.g. ejection fraction less than 30%, pulmonary wedge pressure above 20 mmHg, or severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker (see Section 4.5 Interactions with other medicines and other forms of interactions).

Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment (Note interactions with digoxin under Section 4.5 Interactions with other medicines and other forms of interactions).

Acute Myocardial Infarction:

Use with caution in patients with acute myocardial infarction complicated by bradycardia, marked hypotension, or left ventricular dysfunction.

Hypotension

Occasionally, the pharmacological action of verapamil may produce a decrease in blood pressure below normal levels which may result in dizziness or symptomatic hypotension. The incidence of hypotension observed in 4,954 patients enrolled in clinical trials was 2.5%. In hypertensive patients, decreases in blood pressure below normal are unusual. Tilt table testing (60 degrees) was not able to induce orthostatic hypotension.

Accessory bypass tract (Wolff-Parkinson-White or Lown-Ganong-Levine):

Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a co-existing accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil (or digitalis). Although a risk of this occurring with oral verapamil has not been established, such patients receiving oral verapamil may be at risk and its use in these patients is contraindicated (see Section 4.3 Contraindications).

Treatment is usually DC-cardioversion. Cardioversion has been used safely and effectively after oral verapamil.

Atrioventricular block:

Verapamil affects the AV and SA nodes and prolongs AV conduction time. Use with caution as development of second-or third-degree AV block (contraindication) or unifascicular, bifascicular or trifascicular bundle branch block requires discontinuation in subsequent doses of verapamil hydrochloride and institution of appropriate therapy, if needed.

Verapamil hydrochloride affects the AV and SA nodes and may produce second- or third-degree AV block, bradycardia, and, in extreme cases, asystole. This is more likely to occur in patients with a sick sinus syndrome (SA nodal disease), which is more common in older patients.

Asystole in patients other than those with sick sinus syndrome is usually of short duration (few seconds or less), with spontaneous return to AV nodal or normal sinus rhythm. If this does not occur promptly, appropriate treatment should be initiated immediately.

In studies using Isoptin SR, prolongation of PR interval values of 0.21 to 0.22 sec occurred in 59 of 3,670 patients (=1.6%) and to 0.23 to 0.28 sec in 4 patients whose PR intervals had been normal before treatment (0.1 to 0.2 sec). Second or third degree AV block was not observed. Higher degrees of AV block, however, were infrequently (0.8%) observed.

Patients with hypertrophic cardiomyopathy (IHSS):

In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects were seen: Three patients died in pulmonary oedema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary oedema and/or severe hypotension; abnormally high (over 20 mmHg) capillary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients.

Concomitant administration of quinidine (see Section 4.5 Interactions with other medicines and other forms of interactions) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary oedema). Sinus bradycardia occurred in 11% of the patients, second-degree AV block in 4% and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction and only rarely did verapamil have to be discontinued.

Use in Hepatic Impairment

Since verapamil is highly metabolised by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of immediate release verapamil to about 14 to 16 hours, hence, approximately 30% of the dose given to patients with normal liver

function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see Section 4.9 Overdose) should be carried out.

Elevated liver enzymes:

Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even in the face of continued verapamil treatment. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge. Half of these had clinical symptoms (malaise, fever, and/or right upper quadrant pain) in addition to elevations of SGOT (AST), SGPT (ALT) and alkaline phosphatase. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

Use in patients with impaired neuromuscular transmission:

Verapamil should be used with caution in the presence of diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy).

It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission.

Use in Renal Impairment

About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Verapamil is not removed by haemodialysis. Until further data are available, verapamil should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage (see Section 4.9 Overdose).

Use in the Elderly

Pharmacokinetic data show that the systemic availability of both components of TARKA is higher in elderly compared with young 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 as is careful monitoring of blood pressure when commencing treatment with TARKA 2/180.

Paediatric Use

No data available.

Carcinogenicity and Mutagenicity

Carcinogenicity studies with the trandolapril/verapamil combination have not been performed.

Trandolapril: At least one ACE inhibitor has caused an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential of ACE inhibitors to cause this effect in humans is unknown. Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when it does occur, it is considered to be benign. No carcinogenic effect has been noted in long term rat (24 months, up to 8 mg/kg/day) or mouse (18 months, up to 25 mg/kg/day) studies with trandolapril.

Verapamil: An 18 month toxicity study in rats, at a low multiple (six fold) of the maximum recommended human dose, and not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for two years at doses up to 120 mg/kg/day, approximately 12 times the maximum recommended human daily dose (480 mg/day or 9.6 mg/kg/day).

Neither trandolapril nor verapamil (either alone or in combination) were genotoxic in standard test batteries for gene mutations and chromosomal damage.

Effects on Laboratory Tests

Haematology: Low white cells, low neutrophils, low lymphocytes and low platelets

Serum Electrolytes: Hyperkalaemia, hyponatraemia

Renal Function Tests: Increased creatinine, BUN

Liver Function Tests: Increased SGOT, SGPT, LDH, alkaline phosphatase and/or serum bilirubin

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The section below summarises potential drug interactions between the components of TARKA and other therapeutic agents.

In vitro metabolic studies indicate that verapamil hydrochloride is metabolised by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Verapamil has been shown to be an inhibitor of CYP3A4 enzymes and P-glycoprotein (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 a lowering of plasma levels of verapamil, therefore, patients should be monitored for drug interactions. Coadministration of verapamil and a drug primarily metabolised by CYP3A4 or being a P-gp substrate may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug.

NEP inhibitors

Trandolapril component

Co-administration of ACE inhibitors and NEP inhibitors, e.g. sacubitril (available as fixed-dose combination with valsartan) and racecadotril, is contraindicated as the concomitant inhibition of ACE and neprilysin (neutral endopeptidase, NEP) may increase the risk of angioedema (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use).

Ivabradine

Verapamil component

Concomitant administration of verapamil and ivabradine is contraindicated. Ivabradine use in combination with verapamil is associated with increased plasma concentrations of ivabradine and additional heart rate lowering effects (see Section 4.3 Contraindications).

Dabigatran

Verapamil component

Use of dabigatran with verapamil may increase the bioavailability of dabigatran. Verapamil sustained release: ↑dabigatran (Cmax up to 90% and AUC up to 70%).

When co-administered with oral verapamil, the dose of dabigatran may need to be reduced (refer to dabigatran Product Information for dabigatran dosing instructions) as the risk of bleeding may increase.

No meaningful interaction was observed when verapamil was given 2 hours after dabigatran etexilate (increase of Cmax by about 10% and AUC by about 20%).

Close clinical surveillance is recommended when verapamil is combined with dabigatran etexilate and particularly in the occurrence of bleeding, notably in patients having mild to moderate renal impairment.

Simultaneous initiation of treatment with dabigatran etexilate and oral verapamil is contraindicated (see Section 4.3 Contraindications).

Treatment initiation with oral verapamil in patients following major orthopaedic surgery who are already treated with dabigatran etexilate is contraindicated (see Section 4.3 Contraindications).

Other Direct Oral Anticoagulants (DOACs)

Use of DOACs with verapamil may increase the absorption of DOACs since they are P-glycoprotein (P-gp) substrates. If applicable, coadministration with verapamil may also reduce elimination of DOACs which are metabolised by CYP3A4, and this may increase the systemic bioavailability of DOACs.

When co-administered with oral verapamil, the dose of DOAC may need to be reduced (refer to DOAC Product Information for DOAC dosing instructions) as the risk of bleeding may increase especially in patients with further risk factors.

Heparin

Trandolapril component

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Intravenous beta-blockers

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

Beta-blockers

Verapamil component

Concomitant therapy with beta-adrenergic blockers and verapamil component may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility and induction of heart failure and potentiated hypotension. The addition of beta-blocker therapy (ophthalmic or oral) to patients on verapamil, including TARKA should be done only with caution, and close monitoring.

Trandolapril component

Beta adrenergic blocking drugs will increase the anti-hypertensive effect of ACE inhibitors, therefore the patient will need to be closely supervised.

Antihypertensive Agents

Verapamil component

Verapamil administered concomitantly with oral antihypertensive agents (e.g. vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored.

Concomitant Diuretic Therapy

Trandolapril component

As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with TARKA. The possibility of exacerbation of hypotensive effects with TARKA may be minimised by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with TARKA. If it is not possible to discontinue the diuretic, the starting dose of TARKA should be reduced.

Agents Affecting Serum Potassium

Trandolapril component

Trandolapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. Use of potassium sparing diuretics (spironolactone, triamterene, or amiloride), potassium supplements or potassium containing salt substitutes concomitantly with ACE inhibitors can increase the risk of hyperkalaemia. If concomitant use of such agents is indicated, they should be used with caution and with appropriate monitoring of serum potassium.

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Trandolapril component

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see Section 4.4 Special warnings and precautions for use).

Combination with Angiotensin II Receptor Blockers or Aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use).

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

Trandolapril component

The use of an ACE inhibiting drug (ACE inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Alpha Blockers

Verapamil component

Additive hypotensive effect (e.g. prazosin, terazosin). Concomitant use of agents that attenuate alpha-adrenergic function with verapamil may result in a reduction in blood pressure that is excessive in some patients. Verapamil has been reported to cause the elevation of prazosin plasma levels.

Antiarrhythmics

Verapamil component

When combined with antiarrhythmic drugs mutual potentiation of cardiovascular effects (higher-grade AV block, higher-grade lowering of heart rate, induction of heart failure and potentiated hypotension) may occur.

Quinidine

Verapamil component

In a small number of patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. Pulmonary oedema may occur in patients with hypertrophic obstructive cardiomyopathy with concomitant use of verapamil and quinidine. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided. The electrophysiological effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on AV conduction. There has been a report of increased quinidine levels during verapamil therapy.

Antiasthmatics

Theophylline

Verapamil component

Verapamil therapy may inhibit the clearance and increase the plasma levels of theophylline.

Anticonvulsants

Carbamazepine

Verapamil component

Verapamil may increase carbamazepine concentrations during combined therapy producing carbamazepine side effects such as diplopia, headache, ataxia or dizziness.

Phenytoin

Verapamil component

Verapamil therapy may alter plasma levels of phenytoin.

Antidiabetics

Trandolapril component

Concomitant use of antidiabetic medicines (insulin or oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with greater risk of hypoglycaemia. Therefore, blood glucose should be closely monitored in diabetics treated with a hypoglycaemic agent and trandolapril, particularly when starting or increasing the dose of ACE inhibitor or in patients with impaired renal function.

Vildagliptin

Trandolapril component

Patients taking concomitant vildagliptin may be at increased risk for angioedema.

Anti-infectives

Rifampicin

Verapamil component

Blood pressure lowering effect may be reduced.

Erythromycin, clarithromycin and telithromycin

Verapamil component

Erythromycin, clarithromycin and telithromycin therapy may increase serum levels of verapamil.

Barbiturates

Phenobarbital (phenobarbitone)

Verapamil component

Phenobarbital (phenobarbitone) therapy may increase verapamil clearance.

Benzodiazepines and other anxiolytics

Midazolam

Verapamil component

Verapamil therapy may increase serum levels of midazolam.

Cardiac glycosides

Digoxin

Verapamil component

Clinical use of verapamil in digitalised patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. Chronic verapamil treatment can increase serum digoxin level by 50 – 75% during the first week of therapy, and this can result in digoxin toxicity. Maintenance digoxin doses should be reduced when TARKA is administered, and the patient should be carefully monitored to avoid over- or under-digitalisation. Whenever over digitalisation is suspected, the daily dose of digoxin should be reduced or temporarily discontinued. Upon discontinuation of any verapamil containing regime including TARKA, the patient should be reassessed to avoid under digitalisation.

H2 Receptor Antagonists

Cimetidine

Verapamil component

Possible elevation of verapamil plasma levels.

Immunologics/Immunosuppressants

Ciclosporin

Trandolapril component

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Verapamil component

Verapamil therapy may increase serum levels of ciclosporin.

Mammalian Target of Rapamycin (mTOR) Inhibitors

Trandolapril component

Patients taking concomitant mTOR inhibitor therapy (e.g. temsirolimus, sirolimus, everolimus) may be at increased risk for angioedema.

Verapamil component

Verapamil therapy may increase serum levels of everolimus and sirolimus.

Tacrolimus

Verapamil component

Verapamil therapy may increase serum levels of tacrolimus.

Inhalation Anaesthetics

Verapamil component

Animal experiments have shown that inhalation anaesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anaesthetics and calcium antagonists, such as verapamil, should be titrated carefully to avoid excessive cardiovascular depression.

Trandolapril component

The effects of certain anaesthetics may be enhanced by ACE inhibitors.

Lipid lowering agents

HMG CoA Reductase Inhibitors

Verapamil component

Treatment with HMG CoA Reductase Inhibitors (e.g. simvastatin, atorvastatin or lovastatin) in a patient taking verapamil should be started at the lowest possible dose and titrated upwards. If verapamil treatment is to be added to patients already taking an HMG CoA Reductase Inhibitor (e.g. simvastatin, atorvastatin or lovastatin), consider a reduction in the statin dose and retitrate against serum cholesterol concentrations.

Verapamil may increase serum levels of HMG CoA Reductase Inhibitors primarily metabolised by CYP3A enzymes (e.g. simvastatin and atorvastatin). Similarly, verapamil concentrations may be increased by atorvastatin. Consider using caution when these HMG CoA Reductase Inhibitors and verapamil are concomitantly administered. The concomitant administration of verapamil and high doses of simvastatin has been reported to increase the risk of myopathia/rhabdomyolysis.

Fluvastatin, pravastatin and rosuvastatin are not metabolised by CYP3A4 and are less likely to interact with verapamil.

Metformin

Co-administration of verapamil with metformin may reduce the efficacy of metformin.

Lithium

Verapamil component

Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil-lithium therapy with either no change or an increase in serum lithium levels. However, the addition of verapamil has also resulted in the lowering of serum lithium levels in patients receiving chronic stable oral lithium. Patients receiving both drugs must be monitored carefully.

Trandolapril component

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

HIV antiviral agents

Verapamil component

Due to the metabolic inhibitory potential of some of the HIV antiviral agents, such as ritonavir, plasma concentrations of verapamil may increase. Caution should be used or the dose of verapamil may be decreased.

Sulfinpyrazone

Verapamil component

Blood pressure lowering effect may be reduced.

Neuromuscular Blocking Agents

Verapamil component

Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarising). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Nitrates

Verapamil component

Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacological profile of both drugs and the clinical experience suggest beneficial interactions.

NSAIDS

Trandolapril component

Drugs with prostaglandin synthetase inhibitory properties (e.g. indometacin) may diminish the antihypertensive efficacy of concomitantly administered ACE inhibitors and may increase the risk of hyperkalaemia. As with all antihypertensives, NSAIDs may reduce the antihypertensive effects of trandolapril. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with trandolapril. 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.

NSAIDs including aspirin, unless aspirin is used in lower doses as a platelet aggregation inhibitor, should be avoided with ACE inhibitors in patients with heart failure. The concomitant use of aspirin with verapamil can increase the side effect profile of aspirin (may increase the risk of bleeding).

Antineoplastics

Doxorubicin

Verapamil component

Caution should be used when oral verapamil is administered in combination with doxorubicin due to the potential for increased doxorubicin levels.

Colchicine

Verapamil component

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.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including trandolapril.

Dantrolene

Verapamil component

Hyperkalaemia and myocardial depression have been reported in a coronary artery disease patient treated with verapamil following administration of dantrolene. Combined use of verapamil and dantrolene is not recommended.

Sodium

For TARKA 240 mg/4 mg tablets:

The medicinal product contains 1.6 mmol (or 37.3 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

For TARKA 180 mg/2 mg tablets:

The medicinal product contains 1.2 mmol (or 28.0 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

General

Ethanol (Alcohol)

Verapamil component

Verapamil may inhibit the metabolism of alcohol increasing its CNS depressant effects. Ethanol increases the risk of hypotension.

Trandolapril component

Alcohol increases the bioavailability of ACE inhibitors.

Antacids

Trandolapril component

As antacids decrease the bioavailability of ACE inhibitors, it is recommended that these products are taken separately.

Grapefruit Juice

Verapamil component

Grapefruit juice may increase the plasma levels of verapamil and therefore grapefruit and its juice should not be taken with TARKA.

Other

Trandolapril component

Anaphylactoid reactions to high-flux polyacrylonitrile membranes used in haemodialysis have been reported in patients treated with ACE inhibitors. As with other antihypertensives of this chemical class, this combination should be avoided when prescribing ACE inhibitors to renal dialysis patients.

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide may increase the risk of leukopenia, if used concomitantly with ACE inhibitors.

Agents affecting sympathetic activity (e.g. ganglionic blocking agents or adrenergic neurone blocking agents) may be used with caution.

The antihypertensive effects of ACE inhibitors may be reduced by sympathomimetics. Patients should be carefully monitored.

As with all antihypertensives, combination with a neuroleptic or tricyclic antidepressant increases the risk of orthostatic hypotension.

No pharmacokinetic interaction has been noted when trandolapril was combined with, furosemide or nifedipine. No modification of the anticoagulant properties of warfarin has been observed following simultaneous administration with trandolapril.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

The potential effect of the trandolapril/verapamil combination on fertility has not been evaluated in animal studies.

Trandolapril

Reproduction studies in rats with trandolapril did not show any impairment of fertility at oral doses up to 100 mg/kg/day (600 mg/m2/day), which is ca. 200 times the maximum clinical dose based on body surface area. Reproduction toxicity studies showed effects on renal development in offspring with increased incidence of renal pelvic dilation; this was seen at doses of 10 mg/kg/day and above in the rat but these changes did not affect the normal development of the offspring.

Verapamil

Reproduction studies in female rats with verapamil at daily dietary doses up to 5.5 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

Use in Pregnancy

Pregnancy Category: D

As with all ACE inhibitors, TARKA should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with TARKA and avoided during treatment.

If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment.

If a patient becomes pregnant while on ACE inhibitors, she must immediately inform her doctor to discuss a change in medication and further management.

TARKA is contraindicated during pregnancy, as it carries the potential to product foetal hypoxia associated with maternal hypotension (due to the verapamil component) and may during the second and third trimesters, cause a range of abnormalities (renal dysfunction and oligohydramnios due to the trandolapril component). These effects can be associated with foetal death in utero.

Trandolapril: There are no adequate and well-controlled studies of ACE inhibitors in pregnant women, but foetotoxicity is well documented in animal models. Data however show that ACE inhibitors cross the human placenta. Post marketing experience with all ACE inhibitors suggests that exposure in utero may be associated with hypotension and decreased renal perfusion in the foetus. ACE inhibitors have also been associated with foetal death in utero. As with all ACE inhibitors, when pregnancy is detected, TARKA should be discontinued.

A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to any ACE inhibitor during 1st trimester compared to no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% confidence interval 1.89 to 7.3) and 4.4 times (95% confidence interval 1.37 to 14.02) respectively, compared to no exposure. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of foetal hypotension, renal failure, skull hypoplasia and death.

Oligohydramnios has been reported, presumably resulting from decreased foetal renal function. Oligohydramnios has been associated with foetal limit contractures, craniofacial deformities, hypoplasic lung development and intrauterine growth retardation. Prematurity and patent ductus arteriosus have been reported, however it is not clear whether these events were due to ACE inhibitor exposure or to the mother's underlying disease.

Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. If such complications arise, appropriate medical treatment should be initiated to support blood pressure and renal perfusion.

Verapamil

Reproduction studies have been performed in rabbits and rats at oral doses up to 1.5 (15 mg/kg/day) and six (60 mg/kg/day) times the human oral daily dose, respectively, and have revealed no evidence of teratogenicity. In the rat, however, this multiple of the human dose was embryocidal and retarded foetal growth and development, probably because of adverse maternal effected reflected in the reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. Verapamil hydrochloride crosses the placental barrier and can be detected in umbilical vein blood at delivery. 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.

Use in Lactation

The use of TARKA is contraindicated in breastfeeding.

Verapamil and trandolapril or its metabolites are excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil and trandolapril, nursing should be discontinued while TARKA is administered. Alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Depending on individual susceptibility the patient's ability to drive a vehicle or operate machinery may be impaired, due to blood pressure lowering effects of TARKA, especially in the initial stages of treatment, or when changing over from another drug. Therefore, after the first dose it is not advisable to drive or operate machinery for several hours.

TARKA may increase the blood levels of alcohol and slow its elimination. Therefore the effects of alcohol may be exaggerated.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The listed ADRs have been reported during the clinical phase, the post-marketing surveillance or the phase IV clinical trials.

Reactions During Clinical Trials with fixed dose combination product TARKA (or the Combination of Verapamil + Trandolapril): Adverse events (regardless of causality) which were observed in more than 1 % of patients (regardless of causality) in the double blind phase of eight TARKA® pivotal phase II and III clinical studies (MPF/K9007, MPF/K9301, TV-031-HTN, TV-50-HTN, TV-51-HTN, VT 020, VT 067 and VT 082), or in the open label long-term phase of TV-031-HTN, are depicted in the following table. Within each system organ class, the reactions are ranked under headings of frequency.

The following convention is used for the frequencies: 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). When frequency cannot be estimated from the available data, category frequency: Not known (cannot be estimated from the available data) applies.

MedDRA System Organ Class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known (cannot be estimated from the available data)**
Infections and infestations	Influenza Upper respiratory tract infections	Bronchitis	Herpes simplex		Urinary tract infection Pharyngitis
Blood and lymphatic system disorders		Leukopenia Thrombocytope-nia		Pancytopenia	Agranulocytosis Haemoglobin decreased Haematocrit decreased
Immune system disorders		Hypersensitivity			
Metabolism and nutrition disorders	Hyperlipidae-mia	Hyperkalaemia	Anorexia		Increased appetite Hypercholesterolae-mia Hyperglycaemia Hyponatraemia Hyperuricaemia Gout Enzyme abnormality
Psychiatric disorders		Anxiety		Depression Nervousness Aggression	Insomnia Hallucinations Libido decreased
Nervous system disorders	Headache Dizziness	Tremor Impaired balance Insomnia Paraesthesia Somnolence Syncope		Cerebral haemorrhage Loss of consciousness Hyperaesthesia Dysgeusia	Cerebrovascular accident Myoclonus Migraine Extrapyramidal disorder Paralysis (tetraparesis)
Eye disorders		Abnormal/ blurred vision			Blepharitis Conjunctional oedema Eye disorder
Ear and labyrinth disorders	Vertigo				Tinnitus
Cardiac disorders	Atrioventricu-lar block first degree	AV block complete Angina pectoris Bradycardia Palpitations Tachycardia		Atrial fibrillation Cardiac failure Cardiac arrest	Myocardial infarction Sinus bradycardia Sinus arrest Asystole Arrythmia Ventricular tachycardia Myocardial ischaemia

MedDRA System Organ Class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known (cannot be estimated from the available data)**
					Electrocardiogram abnormal
Vascular disorders	Hypotension Orthostatic hypotension Shock Flushing Hot flushes			Blood pressure fluctuation	Hypertension Angiopathy Peripheral vascular disorder Varicose vein
Respiratory, thoracic and mediastinal disorders	Cough Dyspnoea	Sinus congestion		Asthma	Bronchospasm Upper respiratory tract inflammation Upper respiratory tract congestion Productive cough Pharyngeal inflammation Oropharyngeal pain Epistaxis Respiratory disorder
Gastrointestinal disorders	Constipation Nausea	Diarrhoea Abdominal pain Gastrointestinal disorder Dry mouth		Vomiting Dry throat Pancreatitis	Abdominal discomfort Dyspepsia Gastritis Flatulence Gingival hyperplasia Hematemesis Ileus
Hepatobiliary disorders		Liver function tests abnormal	Hyperbiliru-binaemia	Hepatitis Jaundice Cholestasis	
Skin and subcutaneous tissue disorders		Rash Pruritus Face oedema Hyperhidrosis Stevens-Johnson syndrome Angioedema	Alopecia Skin disorder	Erythema multiforme Psoriasis Dermatitis Urticaria	Toxic Epidermal Necrolysis Purpura Eczema Acne Dry skin
Musculoskeletal and connective tissue disorders	Back pain	Arthralgia Myalgia		Muscular weakness	Pain in extremity Bone pain Osteoarthritis Muscle spasm
Renal and urinary disorders		Increased urinary frequency/ polyuria	Azotaemia		Pollakiuria
Reproductive system and		Impotence		Erectile dysfunction Gynecomastia	Galactorrhoea

MedDRA System Organ Class	Common	Uncommon	Rare	Very rare	Not known (cannot be estimated from the available data)
breast disorders					
General disorders and administration site conditions	Asthenia/ weakness Chest pain	Oedema Fatigue		Oedema peripheral	Pyrexia Feeling abnormal Malaise
Investigations	Alanine aminotransfe-rase increased	Increased LDH Increased alkaline phosphatase Increased serum creatinine Increased BUN Increased SGOT Increased SGPT		Transaminases increased Lipase increased Blood potassium increased Immunoglobulin increased Gamma-glutamyl-transferase increased	Blood prolactin increased

Additional significant adverse events seen with verapamil hydrochloride are listed below by body system:

System Organ Class	Preferred Term
Immune system disorders	Hypersensitivity
Nervous system disorders	Tremor extrapyramidal disorder paralysis (tetraparesis)[1] seizures
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	Atrioventricular block (2°, 3°) Sinus arrest Heart failure may develop or existing heart failure may be exacerbated Sinus bradycardia Asystole
Respiratory, thoracic and mediastinal disorders	Bronchospasm
Gastrointestinal disorders	Gingival hyperplasia Abdominal pain/discomfort
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome Urticaria
Musculoskeletal and connective tissue disorders	Muscular weakness
Reproductive system and breast disorders	Gynecomastia
Investigations	Hyperprolactinaemia Galactorrhea

[1] There has been a single post marketing 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 CYP3A and P-gp inhibition by verapamil. Combined use of verapamil and colchicine is not recommended.

Additional significant adverse events seen with trandolapril are listed below by body system:

System Organ Class	Preferred Term
Blood and lymphatic system disorders	Agranulocytosis
Immune system disorders	Hypersensitivity reactions
Gastrointestinal disorders	Vomiting Abdominal pain Pancreatitis
Skin and subcutaneous tissue disorders	Alopecia
General disorders and administration site conditions	Fever

The following adverse events have been reported with ACE inhibitors as a class:

System Organ Class	Preferred Term
Infections and Infestations	Sinusitis Rhinitis Glossitis
Blood and lymphatic system disorders	Pancytopenia Haemolytic anaemia

System Organ Class	Preferred Term
Psychiatric disorders	Sleep disorder Confusional state
Nervous system disorders	Transient ischaemic attack
Cardiac disorders	Myocardial infarction Cardiac arrest
Vascular disorders	Cerebral haemorrhage
Gastrointestinal disorders	Intestinal angioedema
Hepatobiliary disorders	Cholestasic jaundice
Skin and subcutaneous tissue disorders	Erythema multiforme Toxic epidermal necrolysis
Renal and urinary disorders	Renal failure acute
Investigations	Haemoglobin decreased Haematocrit decreased

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

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

During overdose with TARKA, the following 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 trandolapril/verapamil 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 TARKA overdose should be mainly supportive. Treatment of overdose of the verapamil hydrochloride component includes administration of parenteral calcium, beta adrenergic stimulation and gastrointestinal irrigation have been used in the treatment of verapamil hydrochloride overdose. Due to the potential for delayed absorption of the sustained release product, patients may require observation and hospitalisation for up to 48 hours. Verapamil hydrochloride cannot 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 sulfate). 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Trandolapril

Trandolapril is a long acting, highly lipophilic, non-peptide, angiotensin converting enzyme (ACE) inhibitor with a carboxyl group but without a sulphydryl group. Trandolapril suppresses the plasma renin-angiotensin-aldosterone system. Renin is an endogenous enzyme synthesised 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 (ACE), 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 increases 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 vasodepressive 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 side effects. 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 in 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 up to 48 hours, but trandolapril does not interfere with the circadian blood pressure pattern.

Trandolapril has a sustained effect on blood pressure. Comparing the fall in blood pressure at the steady state trough level of trandolaprilat (i.e. at 24 hours, immediately before the next dose) with that at the steady state peak level, the trough/peak ratio is almost 100 % for a 24-hour period and approximately 70 - 80% for a 48-hour period after a dose. Thus, at steady state, the antihypertensive effect of trandolapril is maintained for up to 48 hours after a dose. Trandolapril is, however, administered as a single daily dose to achieve and maintain effective steady state levels.

Verapamil

Verapamil hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). Verapamil hydrochloride is present as a racemic mixture and different activities reside in the two enantiomers. The pharmacological 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. 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. Verapamil reduces 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 except 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. Asthma and similar conditions, therefore, are not contraindications to verapamil.

TARKA

Neither animal studies nor healthy volunteer studies could demonstrate pharmacokinetic or renin angiotensin system interactions between verapamil and trandolapril. The observed synergistic activity of these two drugs must therefore be due to their complementary pharmacodynamic actions.

In clinical trials, TARKA was more effective in reducing high blood pressure than either drug alone.

TARKA does not adversely influence glucose, insulin or lipid parameters in patients with hypertension and Type II (non-insulin dependent) diabetes mellitus with or without elevated cholesterol and/or triglyceride levels.

TARKA reduces proteinuria to a greater extent than the individual components in patients with diabetic or non-diabetic proteinuria.

Clinical Trials

In controlled clinical trials, once daily doses of TARKA, (trandolapril 4 mg/verapamil SR 240 mg or trandolapril 2 mg/verapamil SR 180 mg), decreased placebo-corrected seated pressure (systolic/diastolic) 24 hours after dosing by about 7-12/6-8 mmHg. Each of the components of TARKA added to the antihypertensive effect. Treatment effects were consistent across age groups (<65, ≥65 years), and gender (male, female). Blood pressure reductions were significantly greater for the TARKA combinations than for either of the respective components used alone. The antihypertensive effects of TARKA have continued during therapy for at least 1 year.

The tabulated results of the pivotal studies involving TARKA 2/180 and TARKA 4/240 are presented below in tables 1 and 2, respectively.

Table 1 - Comparison of adjusted mean blood pressure reduction from baseline SBP/DBP (mmHg) between TARKA 2/180 mg and Trandolapril 2 mg after 12 weeks in patients uncontrolled on Trandolapril 2 mg after 8 weeks of treatment in Study VT067

Treatment	N	Endpoint difference vs. baseline (SBP/DBP)	*P*-value vs. Trandolapril
Trandolapril 2mg	190	-2.3 / - 0.6	
TARKA® 2/180 mg	191	- 8.0 / - 6.1	< 0,001

Table 2 - Comparison between the treatment group and placebo, and between TARKA 240 mg/4 mg and monotherapy agents at endpoint for sitting DBP and SBP (mm Hg) in Study TV-51-HTN

				Endpoint difference vs. monotherapy agents (DBP/SBP)		
Treatment	**N**	**Endpoint difference vs. placebo (DBP/SBP)**	***P*-value vs. placebo**	**vs. verapamil**	**vs. trandolapril**	***P*-value DBP/SBP**
Trandolapril 4 mg	159	-4.5/ -9.0	<0.01			
Verapamil 240 mg	157	-4.3/ -8.0	<0.01			
TARKA® 4/240 mg	163	-8.1/ -12.9	<0.01	-3.8/ -4.9	-3.6/ -3.9	<0.01/<0.01

5.2 PHARMACOKINETIC PROPERTIES

Trandolapril

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

Trandolapril disappears very rapidly from plasma and its half-life is less than one hour. It is hydrolysed in plasma to form trandolaprilat, a specific ACE inhibitor. The time to peak plasma concentration of trandolaprilat is four to six hours and the amount of trandolaprilat formed is independent of food intake. Plasma protein binding of trandolaprilat is 94 %. Trandolaprilat binds with great affinity to ACE and this is a saturable process. Most of the circulating trandolaprilat binds to albumin in a nonsaturable process. Steady state of trandolaprilat, after multiple once daily dosing is reached after about four days in healthy volunteers as well as in younger and elderly hypertensive patients. The effective elimination half-life is 22 hours and the terminal half-life of elimination is between 47 and 98 hours depending on dose. This terminal phase probably represents binding/dissociation kinetics of the trandolapril/ACE complex.

Ten to fifteen percent of an administered trandolapril dose is excreted as unchanged trandolaprilat in urine. Following oral administration of radioactive-labelled trandolapril, 33 % of radioactivity is recovered in urine and 66% 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. Therefore, if treatment with TARKA is desirable it is recommended that the trandolapril dose should be established before starting TARKA. Once the trandolapril dose has been established, the TARKA formulation consistent with the established trandolapril dose should be selected. 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 extraction of trandolaprilat are also increased in cirrhotic patients, albeit to a lesser extent. Trandolapril(at) kinetics are unchanged in patients with compensated hepatic dysfunction.

Verapamil

About 90% of orally administered verapamil is absorbed. Because of rapid biotransformation of verapamil during its first pass through the portal circulation, bioavailability ranges from 20% to 35%. The presence of food has no effect on the bioavailability of verapamil.

The mean time to peak plasma concentration is 4 to 15* hours. The peak plasma concentration of norverapamil is attained about 5 to 15* hours post-dose. Steady state after multiple once daily dosing is reached after three to four days. Plasma protein binding of verapamil is about 90 %.

The mean elimination half-life in single dose studies ranged from 2.8 to 7.4 hours. In these same studies, after repetitive dosing the half-life increased to a range from 4.5 to 12.0 hours (after less than 10 consecutive doses given 6 hours apart). Half-life of verapamil may increase during titration.

Metabolite excretion is in the urine (70 %) and in the faeces (16 %). Norverapamil is one of 12 metabolites identified in urine, has 10 to 20 % of the pharmacological activity of verapamil and accounts for 6% of excreted drug. The steady-state plasma concentrations of norverapamil and verapamil are similar. Verapamil kinetics are not altered by renal function impairment. The bioavailability and elimination half-life of verapamil are increased in patients with liver cirrhosis. Verapamil kinetics are, however, unchanged in patients with compensated hepatic dysfunction. Kidney function has no effect on verapamil elimination.

(* Verapamil Filmtab)

TARKA

As there are no known kinetic interactions between verapamil and trandolapril or trandolaprilat, the single-agent kinetic parameters of these two drugs apply to the combination product as well.

Special Populations

Ethnic differences: In black patients, ACE inhibitors are less effective in lowering blood pressure than in white patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Refer to Section 4.4 Special warnings and precautions for use

Carcinogenicity

Refer to Section 4.4 Special warnings and precautions for use

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Maize starch, lactose monohydrate, povidone, hypromellose, sodium stearylfumarate, microcrystalline cellulose, sodium alginate, magnesium stearate, hyprolose, macrogol 400, macrogol 6000, purified talc, colloidal anhydrous silica, docusate sodium, titanium dioxide, iron oxide red CI 77491, iron oxide yellow CI 77492, iron oxide black CI 77499.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

TARKA 2/180: Packed in PVC/PVDC/aluminium blister packs of 14*, 28, 30*, 50*, 56*, 98*, 280*

TARKA 4/240: Packed in PVC/PVDC/aluminium blister packs of 14*, 28, 30*, 50*, 56*, 98*, 280*

* Not currently marketed in Australia

Australian Register of Therapeutic Goods (ARTG)

AUST R 104663 – TARKA 2/180 trandolapril 2mg & verapamil hydrochloride 180mg tablet blister pack

AUST R 104664 – TARKA 4/240 trandolapril 4mg & verapamil hydrochloride 240mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

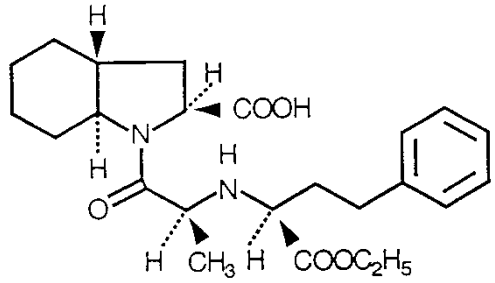
6.7 PHYSICOCHEMICAL PROPERTIES

Trandolapril is a white or almost white, crystalline substance that is soluble in chloroform, dichloromethane and methanol. It is slightly soluble in water and sparingly soluble in hydrochloric acid.

Verapamil hydrochloride is an almost white, crystalline powder, practically free of odour, with a bitter taste. It is soluble in water, freely soluble in chloroform, sparingly soluble in alcohol and practically insoluble in ether.

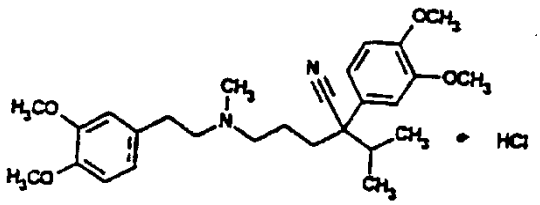
Chemical Structure

Trandolapril



Chemical name: (2S,3aR,7aS)-1-[(2S)-2-[[(1S)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydro-1H-indole-2-carboxylic acid. C24 H34 N2 O5, MW: 430.54

Verapamil



Chemical name: benzeneacetonitrile, α-[3-[{2-(3,4-dimethoxyphenyl)ethyl}methylamino] propyl]-3,4-dimethoxy-α -(1-methylethyl) monohydrochloride. C27H38N204 • HCl, MW: 491.08

CAS Number

Trandolapril: 87679-37-6

Verapamil: 152-11-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Millers Point NSW 2000

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

20/10/2005

10 DATE OF REVISION

11/10/2023

Summary Table of Changes

Section Changed	Summary of New Information
Heading, 4.8	Minor editorial changes
4.5	Remove dual name and retaining sole name only for "furosemide"
4.8	Update to adverse effects reported during the clinical phase, the post-marketing surveillance or the phase IV clinical trials Update to ACEIs' class adverse effects

TARKA® is a registered trademark

TARKA_pi\Oct23/00 (CCDS 25-Jan-2021)