Professional information for TARKA

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

TARKA 180/2 prolonged-release tablet tablets

TARKA 240/4 prolonged-release tablet tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **TARKA 180/2** tablet contains 180 mg verapamil hydrochloride in a sustained release form and 2 mg trandolapril.

Each **TARKA 240/4** tablet contains 240 mg verapamil hydrochloride in a sustained release form and 4 mg trandolapril.

Excipients with known effect:

TARKA 180/2

Contains sugar: 107 mg lactose monohydrate per tablet.

Each tablet contains 25,7 mg sodium.

TARKA 240/4

Contains sugar: 110,37 mg lactose monohydrate per tablet.

Each tablet contains 34,3 mg sodium.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

TARKA 180/2 tablets are pink, oval film-coated tablets, with “182” embossed on one side and plain on the other side.

TARKA 240/4 tablets are red-brown, oval film-coated tablets, with “244” embossed on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TARKA is indicated for the treatment of hypertension in patients not adequately controlled with verapamil or trandolapril alone.

4.2 Posology and method of administration

Posology

Adults:

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

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 the 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, therefore, its use in this group is not recommended.

4.3 Contraindications

- Hypersensitivity to verapamil hydrochloride, trandolapril, another angiotensin-converting enzyme (ACE) inhibitor, or to any of the excipients listed in section 6.1)

- Pregnancy and lactation (see section 4.6)
- History of angioedema associated with administration of an ACE inhibitor or angiotensin-receptor blocker. These patients must never again be given these medicines
- Hereditary or idiopathic angioedema
- Hypotension associated with cardiogenic shock
- Complicated acute myocardial infarction (bradycardia, pronounced hypotension, left ventricular failure)
- Retarded atrioventricular (AV) conduction (second- and third-degree AV block), except in patients with a functioning artificial pacemaker
- Sinoatrial block
- Sick-sinus syndrome (bradycardia-tachycardia syndrome), except in patients with a functioning artificial pacemaker
- Atrial fibrillation/flutter in the presence of an accessory bypass tract (e.g. Wolff-Parkinson-White (WPW) syndrome, Lown-Ganong-Levine syndrome)
- Congestive heart failure
- Concomitant administration of ivabradine
- Moderate to severe liver function impairment
- Moderate to severe renal function impairment (creatinine clearance < 30 L/min)
- Dialysis
- Liver cirrhosis with ascites
- Aortic stenosis, mitral valve stenosis
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Primary aldosteronism
- Bilateral renal artery stenosis or renal artery stenosis in the presence of a single kidney
- Concomitant therapy with potassium sparing diuretics, such as spironolactone, triamterene and amiloride
- Porphyria

 Sign:

- Thiazide diuretics in (fixed dose) combination with TARKA should not be given to patients with Addison's disease. This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide derived medicines
- Lithium therapy: Concomitant administration with TARKA may lead to toxic blood concentrations of lithium
- Administration to children and adolescents (< 18 years old)
- Patients treated concomitantly with intravenous beta-receptor blockers (exception: intensive care unit patients)
- Concomitant administration of TARKA with medicines containing aliskiren is contraindicated in patients with diabetes mellitus or impaired kidney function (GFR < 60 mL/min/1,73 m^2) (see section 4.4 and 4,5)
- Concomitant administration of sacubitril/valsartan therapy. Treatment with TARKA should be initiated at least 36 hours after the last dose of sacubitril/valsartan (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving TARKA, the treatment must be stopped promptly and changed to a different medicine.
Should a woman contemplate pregnancy, the doctor should consider alternative medication (see section 4.6).

TARKA should not be used in patients with aortic stenosis or outflow obstruction.

Symptomatic hypotension:

TARKA may occasionally produce symptomatic hypotension in normotensive patients. TARKA may occasionally produce symptomatic hypotension, and this risk is elevated in patients with an activated renin-angiotensin-aldosterone system, for instance in the following conditions:

- fluid or salt depletion, for instance due to the use of diuretics, a low-sodium diet, dialysis, dehydration, diarrhoea or vomiting;
- cardiac insufficiency;
- liver cirrhosis with ascites (see section 4.3).

In hypertensive patients, decreases in blood pressure below normal values are unusual.

Renovascular hypertension has been observed in patients with reduced left ventricular function.

Such patients should have their fluid or salt depletion corrected beforehand and preferably be started on an ACE inhibitor in a hospital setting. Patients experiencing a hypotensive reaction during the titration phase should lie down and may require blood volume expansion by oral fluid replacement therapy or intravenous administration of normal saline.
TARKA treatment can usually be continued once blood volume and blood pressure have been effectively corrected.
Strict monitoring is essential at the start of treatment and on adjusting the dosage in patients with ischaemic heart disease or cerebrovascular disease in whom an excessive drop in blood pressure may lead to a myocardial infarction or cerebrovascular event.

Impaired kidney function

Changes in renal function are not usually observed during TARKA therapy. Patients with impaired renal function require regular monitoring of kidney function and it may be necessary to discontinue treatment with the fixed combination in these patients.

TARKA may produce hyperkalaemia in hypertensive patients, especially those with renal impairment.
Acute deterioration of kidney function (acute renal failure) may occur especially in patients with pre-existing renal impairment, congestive heart failure, or renovascular hypertension, particularly in patients with bilateral renal arterial stenosis or unilateral renal artery stenosis in individuals with

a sole (functioning) kidney, such as renal transplant patients for instance (see section 4.3). Concurrent diuretic therapy may be a contributing factor. Regular monitoring of kidney function is therefore recommended for these groups of patients.

Renovascular hypertension:

Only limited experience has been acquired to date when using TARKA to treat patients with secondary hypertension and renovascular hypertension in particular. Therefore, these patients should not be given TARKA. An increase in urea and serum creatinine levels in the blood was observed in some patients with bilateral renal artery stenosis or unilateral renal artery stenosis and treated with ACE inhibitors. This was generally reversible on discontinuation of treatment. This is particularly likely in patients with kidney failure. There is also an increased risk of severe hypotension and kidney failure in patients presenting with renovascular hypertension.

Proteinuria:

Proteinuria may occur especially in patients with existing renal impairment or those treated with relatively high doses of an ACE inhibitor.

Diabetic patients:

Glycaemic status should be strictly controlled during the first month of treatment with an ACE inhibitor in diabetic patients receiving antidiabetic medicine or insulin (see section 4.5).
Dual blockade of the renin angiotensin aldosterone system (RAAS):
There is evidence that concomitant administration of ACE inhibitors, angiotensin II receptor antagonists or aliskiren increases the risk of hypotension and hyperkalaemia, and reduces kidney function (including acute kidney failure). Dual blockade of the RAAS through the concomitant use of ACE inhibitors, angiotensin II receptor antagonists or aliskiren is therefore not recommended (see sections 4.5 and 5.1). If dual blockade therapy is considered absolutely essential, this should only be administered under expert supervision and strict monitoring of kidney function, electrolyte

values and blood pressure. ACE inhibitors and angiotensin II receptor antagonists should not be administered concomitantly to patients with diabetic nephropathy.

Impaired liver function:

As trandolapril is a prodrug metabolised to its active moiety in the liver, particular caution and close monitoring should be applied to patients with impaired liver function.
Since verapamil is highly metabolised by the liver, TARKA should be administered cautiously to patients with impaired hepatic function.

TARKA is not recommended given the lack of therapeutic experience in patients with severe liver impairment. TARKA is contraindicated in patients presenting with severe cirrhosis of the liver accompanied by ascites (see section 4.3). Very occasionally, treatment with an ACE inhibitor is associated with a syndrome that starts with cholestatic jaundice or hepatitis, advances to fulminating necrosis and sometimes proves fatal. The mechanism of this syndrome is unknown. TARKA should be discontinued, and medical follow-up initiated in patients who develop jaundice or present with a marked rise in liver enzyme values.

Elevated liver enzymes:

Elevation of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin has been reported. Such elevations are normally transient and may disappear even in the face of continued TARKA treatment.

Angioedema:

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors and angiotensin-receptor blockers. In such cases TARKA should be discontinued immediately and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confirmed to the face and lips, the condition generally resolved without

treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal/glottis oedema may be fatal due to constriction of the airways.

ACE inhibitors have been shown to cause a higher rate of angioedema in black patients than in non-black patients.

Concomitant administration of ACE inhibitors and sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Sacubitril/valsartan may only be administered 36 hours after the last dose of the trandolapril therapy, as contained in TARKA. Treatment with TARKA may only be initiated 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant administration of ACE inhibitors and racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may increase the risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory difficulties) (see section 4.5). Caution should be exercised when treatment with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin is initiated in patients already taking an ACE inhibitor.

Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy such as subcutaneous epinephrine (adrenaline) solution 1:1000 (0,3 mL to 0,5 mL) should be administered promptly.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. TARKA is contraindicated when angioedema is an existing adverse effect of ACE inhibitor treatment (see also section 4.3).

Intestinal angioedema:

Sign:

Intestinal angioedema has been reported in patients treated with ACE inhibitors. This should be taken into account in patients treated with trandolapril, as in TARKA, and presenting with abdominal pain (with or without nausea or vomiting).

Agranulocytosis and bone marrow depression:

In patients on ACE inhibitors agranulocytosis and bone marrow depression have been seen rarely. The risk of neutropenia appears to be dose and type dependent. It also depends on the patient's clinical condition. Neutropenia is rarely observed in patients who are complication-free but may develop in those with a certain degree of kidney dysfunction especially when the latter is accompanied by collagen diseases, such as systemic lupus erythematosus, scleroderma, and immunosuppressant therapy. The condition is reversible on discontinuation of the ACE inhibitor. However, regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (e.g., lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy, particularly with corticosteroids and antimetabolites.

Cough:

Dry, non-productive cough may develop during treatment with an ACE inhibitor. This disappears once the medicine is discontinued.

Serum potassium:

ACE inhibitors may trigger hyperkalaemia as they prevent the release of aldosterone. The effect is generally insignificant in patients with normal kidney function. However, hyperkalaemia may develop in patients with impaired kidney function and/or those taking potassium supplements (including salt supplements), potassium-sparing diuretics, trimethoprim or cotrimoxazole (also known as trimethoprim/sulfamethoxazole) and aldosterone antagonists or angiotensin-receptor blockers in particular. Concomitant use with potassium-sparing diuretics is contraindicated (see section 4.3). Caution should be exercised when administering angiotensin-receptor blockers to

patients taking ACE inhibitors. Potassium serum levels and kidney function should be monitored (see section 4.5).

Elderly patients:

TARKA has been studied in only a limited number of elderly hypertensive patients. The available 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. Kidney function should be tested at the start of treatment.

Surgery/anaesthesia:

ACE inhibitors may lead to hypotension in patients requiring general anaesthesia due to major surgery. In patients undergoing surgery or during anaesthesia with medicines producing hypotension, TARKA may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs it can be corrected by appropriate treatment. This can be corrected with plasma expanders.

Heart failure:

TARKA should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction less than 30 %, pulmonary pressure above 20 mm HG or severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker. In patients with episodes of heart failure, the ejection fraction should be higher than 35 % before treatment with TARKA is initiated. Adequate therapy should then be administered (see section 4.3).

Accessories bypass tract (Wolff-Parkinson-White or Low-Ganong- Levine):

Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have developed an increased anterograde 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 TARKA has not been established, such patients receiving TARKA may be at risk (see section 4.3).

First degree atrioventricular (AV) block:

Verapamil affects AV and SA nodes and prolongs AV conduction time. Caution should be exercised in patients with first degree atrioventricular block. Please note that the use of TARKA is contraindicated in the case of second- and third-degree AV block (see section 4.3).

Bradycardia:

TARKA should be administered with caution to patients with bradycardia.

Patients with hypertrophic obstructive cardiomyopathy:

A variety of serious adverse effects can occur in patients with hypertrophic obstructive cardiomyopathy – pulmonary oedema and/or severe hypotension, sinus bradycardia, AV block and sinus arrest.

Neuromuscular transmission disorders:

TARKA should be administered with caution to patients with diseases in which neuromuscular transmission is adversely affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne's muscular dystrophy).

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

Desensitisation:

Anaphylactoid reactions (in some cases life-threatening) may develop in patients receiving ACE inhibitor therapy and desensitisation therapy against animal venoms at the same time.

LDL apheresis:

Life-threatening anaphylactoid reactions have been noted when patients receiving LDL-apheresis therapy take ACE inhibitors at the same time. Kidney function tests should be carried out before and during treatment.

Blood pressure should always be recorded before starting the next dose in order to assess the therapeutic response to TARKA.

Lithium:

The concomitant administration of lithium and TARKA is contraindicated (see section 4.3 and 4.5).

Beta-blockers:

Concomitant administration with beta-receptor blockers can potentiate the cardiovascular effects (severe AV block, marked reduction in heart rate, onset of heart failure, increased hypotension). Asymptomatic bradycardia (36 beats per minute) was observed in one patient taking timolol (a beta-blocker) eye drops concomitantly and fitted with a migrating atrial pacemaker (see section 4.5).

Digoxin:

Increased blood concentrations of digoxin have been reported following the concomitant administration of digoxin and verapamil, as in TARKA (see section 4.5). Digoxin dose levels should be reduced if required.

HMG CoA reductase inhibitors ("statins"):

An increased risk of myopathy/rhabdomyolysis has been reported following concomitant administration of verapamil, as in TARKA, and high doses of simvastatin. Dose levels of simvastatin (and other statins metabolised by CYP3A4 such as atorvastatin and lovastatin) should be adjusted accordingly (see section 4.5).

Pregnancy:

ACE inhibitor therapy should not be initiated during pregnancy. If continued ACE inhibitor therapy is not 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 during breastfeeding (see section 4.6).

Lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take TARKA.

Sodium:

TARKA 180/2 contains 25,7 mg sodium per tablet equivalent to 1,29 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
TARKA 240/4 contains 34,3 mg sodium per tablet, equivalent to 1,72 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Interactions with other medicines may occur due to pharmacodynamic or pharmacokinetic interaction or both. In cases where events are associated with both pharmacodynamic and pharmacokinetic interactions, a cross-reference to the relevant section is included.

Concomitant administration is not recommended with:

Medicines that increase the risk of angioedema:

The simultaneous administration of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see sections 4.3 and 4.4). Concomitant administration of ACE inhibitors and racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin can lead to an increased risk of angioedema (see section 4.4).

Potassium-sparing diuretics, potassium supplements or potassium-containing salt supplements:

Hyperkalaemia may occur in some patients receiving TARKA although serum potassium levels are generally within the normal range. Potassium-sparing diuretics (such as spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt supplements may significantly increase serum potassium levels. Concomitant use with potassium-sparing diuretics is contraindicated (see section 4.3). Caution should also be exercised if TARKA is administered concomitantly with other medicines that increase serum potassium levels, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) because trimethoprim is known to function like a potassium-sparing diuretic, such as amiloride. Combination therapy comprising TARKA and the aforementioned medicines is therefore not recommended. If concomitant administration is indicated, caution should be exercised and serum potassium levels monitored on a regular basis.

Ciclosporin:

Hyperkalaemia may occur following concomitant administration of ACE inhibitors and ciclosporin. Serum potassium levels should be monitored.

Heparin:

Hyperkalaemia may occur following concomitant administration of ACE inhibitors and heparin. Serum potassium levels should be monitored.

Angiotensin II receptor antagonists or aliskiren:

Data from clinical studies have shown that dual blockade of the renin angiotensin aldosterone system (RAAS) is associated with an increased incidence of adverse events, such as hypotension, hyperkalaemia and reduced kidney function (including acute kidney failure) during concomitant administration of ACE inhibitors, angiotensin II receptor antagonists or aliskiren compared to administration of a single substance having an effect on RAAS (see sections 4.3, 4.4 and 5.1).

***Dantrolene*:**

Concomitant administration of verapamil and dantrolene is not recommended.

Ivabradine:

Concomitant administration with ivabradine is contraindicated due to the additional heart rate lowering properties of verapamil and ivabradine (see section 4.3).

Antiviral HIV medicine:

Verapamil plasma levels may rise due to the metabolism-inhibiting potential of some antiviral HIV medicines, such as protease inhibitors including ritonavir. They should therefore be used with caution or the verapamil dose should be reduced.

***Lithium*:**

Both an increase and a reduction in lithium efficacy have been reported during concomitant administration of verapamil, as in TARKA. Combined treatment with ACE inhibitors and lithium can reduce the elimination of lithium. Serum lithium levels (increased lithium neurotoxicity) should be frequently monitored (see section 4.4).

Intravenously injected beta-blockers:

Intravenously injected beta-blockers should not be administered during TARKA therapy (see section 4.3). Concomitant administration of verapamil and beta-blockers may lead to severe atrioventricular conduction disorders, possibly culminating in severe bradycardia in some cases. Severe cardiac depression may also occur.

Colchicine:

Colchicine is a substrate for both CYP3A and the efflux transporter P-glycoprotein (P-gp). Verapamil inhibits CYP3A and P-gp. Verapamil-induced inhibition of P-gp 380 and/or CYP3A may lead to increased colchicine exposure during the concomitant administration of verapamil and colchicine. Therefore, concomitant administration is not recommended.

***Gold*:**

Nitritoid reactions (symptoms include facial inflammation, nausea, vomiting and hypotension) have very occasionally been reported in patients injected with gold (sodium aurothiomalate) and treated with ACE inhibitors, such as TARKA, at the same time.

Special warnings and precautions for use:

***Antihypertensives*:**

Potentiation of the hypotensive effect of TARKA (see pharmacokinetic interactions with verapamil below). TARKA may enhance the effect of other antihypertensive medicines.

***Diuretics*:**

In patients receiving diuretic therapy, and especially those with fluid and/or salt depletion, the introduction of ACE inhibitor therapy, such as TARKA, may trigger excessive hypotension. The risk of an excessive hypotensive effect can be reduced by stopping the diuretic, increasing fluid

and salt intake prior to taking TARKA, or by lowering the initial dose. Caution should be exercised if the dose is further increased.

If it is necessary to continue the diuretic treatment, the patient should be monitored, at least after the initial administration of TARKA. Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia particularly in renal failure. Trandolapril in TARKA may attenuate the potassium loss caused by thiazide-type diuretics (see section 4.3). Concomitant use with potassium-sparing diuretics is contraindicated (see section 4.3). If concomitant use of TARKA with other diuretics is indicated, they should be given with caution and serum potassium should be monitored regularly. Some hypertensive patients with no apparent pre-existing renal disease may develop increases in blood urea nitrogen and serum creatinine when TARKA is given concomitantly with a diuretic.

Anaesthetics:

TARKA may potentiate the hypotensive effect of certain anaesthetics.

Narcotics/antipsychotic medicines:

Orthostatic hypotension may occur.

Sedatives/antidepressant medicines:

As with all antihypertensive medicines, the risk of orthostatic hypotension is increased when TARKA is administered concomitantly with strong sedatives or imipramine-containing antidepressant medicines (see pharmacokinetic interactions with verapamil).

Allopurinol, cytostatic medicines or immunosuppressants, systemic corticosteroids or procainamide:

Concomitant treatment with ACE inhibitors may increase the risk of leucopoenia (see pharmacokinetic interactions with verapamil below).

Medicines with a cardiodepressive effect:

The concomitant administration of verapamil in TARKA, and medicines with a cardiodepressive effect, i.e. active substances that attenuate cardiac impulse generation and stimulus conduction (e.g. beta-blockers, antidysrhythmic medicines, inhalation anaesthetics) may trigger adverse additive effects (see pharmacokinetic interactions with verapamil below).

Quinidine:

In a few cases, the concomitant administration of quinidine and oral verapamil has led to hypotension and pulmonary oedema in patients with hypertrophic (obstructive) cardiomyopathy (see pharmacokinetic interactions with verapamil below). Until further data are obtained, combined therapy of TARKA and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

Digoxin and digitoxin:

A 50 – 75 % increase in plasma digoxin levels has been reported following concomitant administration of digoxin and verapamil. This subsequently warrants a reduction in digoxin and digitoxin dose levels. Verapamil also reduces the total body clearance and extrarenal clearance of digitoxin by 27 % and 29 %, respectively (see pharmacokinetic interactions with verapamil below).

Dabigatran:

Concomitant administration of verapamil with dabigatran will presumably lead to elevated dabigatran plasma concentrations. Caution should be exercised due to the risk of bleeding. Elevated dabigatran C_{max} and AUC levels were recorded following concomitant administration of dabigatran etexilate (150 mg) and oral verapamil. The extent of this interaction depends on the time of administration and the verapamil formulation. Dabigatran exposure was increased following administration of a prolonged-release formulation of verapamil 240 mg (C_{max} and AUC levels increased by approximately 90 % and 70 %, respectively). Close clinical monitoring is

recommended when verapamil, as in TARKA, is combined with dabigatran etexilate, especially in the event of bleeding and particularly in patients with mild to moderate renal impairment.

Other direct oral anticoagulants (DOACs):

The systemic bioavailability of DOACs, which are substrates for P-gp and/or metabolised by CYP3A4, is expected to be increased when verapamil is administered concomitantly. Data suggest a possible increase in the risk of bleeding, especially in patients with risk factors. The dose of DOAC with verapamil, as in TARKA, may need to be reduced (see DOAC label for dosing instructions).

Muscle relaxants:

The effect of muscle relaxants (e.g. neuromuscular blockers) may be potentiated. It may be necessary to decrease the dose of TARKA and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Points to note:

Non-steroidal anti-inflammatory drugs (NSAIDs):

As with all antihypertensive medicines, the administration of NSAIDs (including acetylsalicylic acid at high doses as an anti-inflammatory medicine, e.g. in pain relief) may reduce the antihypertensive effect of trandolapril. Blood pressure monitoring should be increased at the start and end of NSAID therapy in patients treated with trandolapril, as in TARKA. Furthermore, it has been described that NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium levels whereas renal function may decrease. These effects are generally reversible and occur especially in patients with impaired renal function.

The use of NSAIDs including acetylsalicylic acid (except when acetylsalicylic acid is administered at a lower dose as an antiplatelet medicine) in conjunction with ACE inhibitors should be avoided in patients with heart failure. The concomitant administration of aspirin (acetylsalicylic acid) and

verapamil, as in TARKA, may potentiate the side effect profile of aspirin (acetylsalicylic acid) (increased risk of bleeding).

Antacids:

May reduce the bioavailability of ACE inhibitors.

Sympathomimetic medicines:

May reduce the antihypertensive effect of ACE inhibitors. Patients should be carefully monitored in order to check whether the desired effect is obtained.

Alcohol:

Alcohol potentiates the hypotensive effect of TARKA. Concomitant use of TARKA with ethanol (alcohol) may result in elevated ethanol plasma levels.

Antidiabetic medicines:

Concomitant use of antidiabetic medicines (insulin or oral hypoglycaemic medicines) may cause an increased blood glucose lowering effect with greater risk of hypoglycaemia.The dose of antidiabetic medicines or TARKA may have to be adjusted at the start of treatment (see section 4.4).

Metformin:

Concomitant administration of verapamil and metformin can adversely affect the efficacy of metformin.

mTOR inhibitors (e.g. sirolimus, everolimus and temsirolimus):

The risk of developing angioedema may be increase in patients treated concomitantly with mTOR inhibitors (see section 4.4).

Pharmacokinetic interactions with verapamil, as in TARKA:

In-vitro studies indicate that verapamil, as in TARKA, is metabolised by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Verapamil has been shown to be 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 lowered verapamil plasma levels. Patients should therefore be monitored for interactions. Co-administration of verapamil and a concomitant medicine primarily metabolised by CYP3A4 or a P-gp substrate may be associated with elevations in medicine concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant medicine.

Examples of such interactions are:

Verapamil can increase the plasma levels of:

Almotriptan, buspirone, carbamazepine (enhanced neurotoxicity), ciclosporin, digoxin, digitoxin, direct oral anticoagulants (e.g. dabigatran, rivaroxaban), doxorubicin, everolimus, glibenclamide, imipramine, metoprolol, midazolam, prazosin, propranolol, quinidine, sirolimus, tacrolimus, terazosin and theophylline. Consequently, the toxicity risk of these medicines may be increased. Dose adjustment or additional monitoring of plasma levels should be considered, if required.

HMG CoA reductase inhibitors:

An increase in simvastatin (metabolised by CYP3A4) plasma levels has been reported following the concomitant administration of verapamil, as in TARKA. An increased risk of myopathy/rhabdomyolysis has been reported with the concomitant administration of verapamil and high dose levels of simvastatin. Simvastatin dose levels (and those of other statins, such as atorvastatin and lovastatin, which are metabolised by CYP3A4) should be adjusted accordingly.

Verapamil concentrations may be increased by:

Verapamil concentrations may be increased by atorvastatin, cimetidine, clarithromycin, erythromycin and telithromycin. Macrolide antibiotics when used concomitantly with TARKA may result in increased verapamil levels. Grapefruit juice increases the plasma levels of verapamil,

one of the medically active substances of TARKA. Therefore, TARKA should not be taken with grapefruit juice.

Verapamil concentrations may be lowered by:

Phenytoin, phenobarbital, rifampicin, sulfinpyrazone and medicines containing St John's Wort.

Other:

TARKA has been given concomitantly with short-and long-acting nitrates without any undesirable interactions.

Cytostatic or immunosuppressive medicines or systemic corticosteroids may increase the risk of leucopenia, if used concomitantly with TARKA.

Anaphylactoid reactions to high-flux polyacrylonitrile membranes used in haemodialysis have been reported in patients treated with ACE inhibitors including TARKA, and should be avoided in renal dialysis patients.

Until data on possible interactions between verapamil in TARKA and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after TARKA administration. A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil in TARKA might have additive effects on myocardial contractility, AV conduction and repolarisation. This may result in additive negative inotropic effect and prolongation of AV conduction.

4.6 Fertility, pregnancy and lactation

TARKA is contraindicated in pregnancy and lactation.

Pregnancy:

Should a woman become pregnant while receiving TARKA, the treatment must be stopped promptly and changed to a different medicine.

Should a woman contemplate pregnancy, the doctor should consider alternative antihypertensive medicines which have an established safety profile for use in pregnancy (see sections 4.3 and 4.4).

Epidemiological data 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 the risk cannot be excluded. When pregnancy is diagnosed, treatment with TARKA should be stopped immediately and, if appropriate, alternative therapy should be started.

The trandolapril in TARKA passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios, decreased renal function, skull ossification retardation as well as renal failure, hyperkalaemia, hypotension, oliguria and anuria in newborns have been reported in the second and third trimester. Cases of defective skull ossification have been observed. Premature and low birth mass can occur. The verapamil in TARKA crosses the placental barrier and can be detected in umbilical vein blood at delivery. Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the 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 pregnancy. Also, foetal bradycardia and hypotension cannot be excluded, based on the pharmacological properties.

Lactation:

The verapamil in TARKA is excreted in human breast milk. There is no information available regarding the excretion of trandolapril into human breast milk.

TARKA is not recommended for nursing mothers and alternative antihypertensive treatments with better established safety profiles during lactation are preferable, especially while nursing a new-born or premature infant. Breastfeeding should be discontinued during TARKA therapy. (See section 4.3)

Sign:

4.7 Effects on ability to drive and use machines

Depending on individual susceptibility, the patients' ability to drive a vehicle or operate machinery may be impaired, especially in the initial stages of treatment. TARKA may increase the blood levels of alcohol and slow its elimination. Therefore, the effects of alcohol may be exaggerated.

4.8 Undesirable effects

Summary of the safety profile:

The undesirable effects related to TARKA correspond to those associated with the substances or respective medicines category. The most common undesirable effects are cough, headaches, constipation, vertigo, dizziness and hot flushes (see table below).

The following adverse reactions have been reported in long-term clinical trials with TARKA. The events are displayed by system organ class and frequency, using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000). Adverse event terms are listed in MedDRA terminology.

System organ class	Common	Uncommon	Rare	Very rare
Infections and infestations			Herpes simplex	Bronchitis
Blood and lymphatic system disorders				Pancytopenia Leucopenia Thrombocytopenia
Immune system disorders		Allergic reactions, nonspecific		
Metabolism and nutrition disorders		Hyperlipidaemia	Anorexia	

Sign:

Psychiatric disorders				Depression Nervousness Anxiety Aggression Insomnia
Nervous system disorders	Headache Dizziness	Tremor Somnolence	Syncope	Cerebral haemorrhage Loss of consciousness Balance disorder Hyperaesthesia Paraesthesia Dysgeusia
Eye disorders				Visual impairment Blurred vision
Ear and labyrinth disorders	Vertigo			
Cardiac disorders	Grade 1 AV block	Palpitations		Angina pectoris Bradycardia Tachycardia Atrial fibrillation Heart failure Cardiac arrest
Vascular disorders	Hypotension# Orthostatic hypotension Shock Flushing (flush syndrome) Hot flushes			Blood pressure fluctuation

Sign:

Respiratory, thoracic and mediastinal disorders	Cough			Asthma Dyspnoea Sinus congestion
Gastrointestinal disorders	Constipation	Nausea Diarrhoea Abdominal pain Non-specific gastrointestinal disorders		Vomiting Dry throat Dry mouth Pancreatitis
Hepatobiliary disorders		Abnormal liver values	Hyperbilirubinemia	Hepatitis Jaundice Cholestasis
Skin and subcutaneous tissue disorders		Rash Pruritus Face oedema Hyperhidrosis	Alopecia Non-specific skin disorders	Angioedema Erythema multiforme Dermatitis Psoriasis Urticaria
Musculoskeletal and connective tissue disorders			Arthralgia Myalgia Myasthenia	
Renal and urinary disorders		Polyuria	Azotaemia	Acute renal failure*
Reproductive system and breast disorders			Impotence Gynaecomastia	
General disorders and		Chest pain		Oedema Peripheral oedema

Sign:

administration site conditions				Asthenia Fatigue
Investigations		Abnormal liver function test		Increased transaminase levels Increased alkaline phosphatase levels in the blood Increased LDH levels in the blood Increased lipase Increased serum potassium levels Increased immunoglobulin Increased gamma-GT

[#] Symptomatic or severe hypotension can occasionally occur following the introduction of ACE inhibitor therapy, especially in certain risk groups such as patients with an activated renin angiotensin aldosterone system. Verapamil treatment can lead to myocardial infarction or cerebrovascular episodes in patients with angina pectoris or cerebrovascular diseases.

* Adverse reactions of the ACE inhibitor active substance category.

Post-marketing experience:

System organ class	**Frequency unknown**
Infections and infestations	Infections of the upper airways Pharyngitis Sinusitis* Rhinitis* Glossitis* Urinary tract infection

Sign:

Blood and lymphatic system disorders	Agranulocytosis Reduction in haemoglobin* and haematocrit*, Haemolytic anaemia*[1]
Metabolism and nutrition disorders	Increased appetite Hyperkalaemia Hypercholesterolaemia Hyperglycaemia Hyponatraemia Hyperuricaemia Gout Enzyme anomalies
Psychiatric disorders	Sleep disorders* Hallucinations Diminished libido Confusion*
Nervous system disorders	Transient ischemic attacks* Stroke Myoclonia Migraine Extrapyramidal disorders**[7] Paralysis (tetraparesis)**[6]
Eye disorders	Blepharitis Conjunctival oedema Eye disorder
Ear and labyrinth disorders	Tinnitus*
Cardiac disorders	Myocardial infarction*[2] 2nd and 3rd degree AV block Sinus bradycardia Sinus arrest Asystole

Sign:

	Arrhythmia*[2] Ventricular tachycardia Myocardial ischemia Abnormal ECG
Vascular disorders	Hypertension Angiopathy Peripheral arterial occlusive disease Varicose veins Cerebral haemorrhage*
Respiratory, thoracic and mediastinal disorders	Bronchospasm* Inflammation of the upper airways Swelling of the upper airways Productive cough Oropharyngeal pain Epistaxis Respiratory tract disorders
Gastrointestinal disorders	Abdominal discomfort Dyspepsia* Gastritis Flatulence Gingival hyperplasia**[5] Haematemesis Ileus* Intestinal angioedema* Glossitis*
Hepatobiliary disorders	Cholestatic jaundice*
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome Toxic epidermal necrolysis*[3] Erythromelalgia** Purpura

Sign:

	Eczema Acne Dry skin
Musculoskeletal and connective tissue disorders	Backache Pain in the extremities Painful bones Arthrosis Muscle spasms Myasthenia gravis**[7]
Renal and urinary disorders	Pollakisuria / increased urinary frequency
Reproductive system and breast disorders	Galactorrhoea**
General disorders and administration site conditions	Pyrexia Abnormal condition Malaise
Investigations	Increased creatinine blood levels*[4] Increased blood urea levels*[4] Increased prolactin blood levels** Increased liver enzymes (including ALT and AST)

* Adverse reactions of the ACE inhibitor active substance category.

** Adverse reactions not yet reported in relation to TARKA but generally associated with phenylalkylamine calcium channel blockers.

1: Haemolytic anaemia has been reported in patients with glucose-6-phosphate-dehydrogenase deficiency.

2: Isolated reports of arrhythmia and myocardial infarction during treatment with ACE 607 inhibitors in conjunction with hypotension.

3: Signs of hypersensitivity such as, for instance, toxic epidermal necrolysis. This may be associated with fever, myalgia, arthralgia, eosinophilia and/or elevated ANA titres.

4: Especially in patients with kidney failure, severe heart failure or renovascular hypertension. These are reversible on discontinuation of medicine.

5: Extremely rare in the case of long-term therapy and reversible following discontinuation of treatment.

6: Individual reports of paralysis (tetraparesis) following concomitant administration of verapamil and colchicine in a post-marketing study. Concomitant administration of verapamil and colchicine is not recommended (see section 4.5).

7: Some cases of extrapyramidal disorders (e.g. Parkinson's disease, choreoathetosis, dystonia) have been reported. Experience gained to date confirms that these symptoms disappear as soon as this medication is discontinued. There have been isolated reports of myasthenia gravis, myasthenia syndrome (e.g. Lambert-Eaton syndrome) and advanced stages of muscular dystrophy, e.g. Duchenne.

Additional significant adverse events seen with verapamil hydrochloride are listed below by system organ class, and may also occur with TARKA:

Immune system disorders: Hypersensitivity.

Cardiac disorders: Atrioventricular block (first-, secondary- and third-degree heart block), sinus arrest. Heart failure may develop or existing heart failure may be exacerbated.

Gastrointestinal disorders: Gingival hyperplasia, abdominal pain/discomfort.

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, urticaria.

Reproductive system and breast disorders: Gynaecomastia.

Investigations: Hyperprolactinaemia, galactorrhoea.

Additional significant adverse events seen with trandolapril are listed below by system organ class and may occur with TARKA:

Blood and lymphatic system disorders: Agranulocytosis.

Immune system disorders: Hypersensitivity reactions.

Gastrointestinal disorders: Vomiting, abdominal pain.

Skin and subcutaneous tissue disorders: Alopecia.

General disorders and administration site conditions: Fever.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TARKA is important. It allows continued monitoring of the benefit/risk balance of TARKA. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms:

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

During overdose with TARKA, the following symptoms may occur due to the trandolapril component: severe hypotension, shock, dizziness, stupor, bradycardia, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, vertigo, anxiety and cough.

Treatment:

In the event of overdosage following recent ingestion, emptying of the stomach contents should be considered. Due to the potential for delayed absorption of the sustained release formulation, patients may require observation and hospitalisation for up to 48 hours.

Further absorption of verapamil present in the gastrointestinal tract should be prevented by 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 overdosage is symptomatic and supportive.
Treatment of overdosage of the verapamil component in TARKA includes 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 should be monitored in hospital for up to 48 hours. The verapamil component of TARKA cannot be removed by haemodialysis.

The recommended treatment of a trandolapril overdose is intravenous infusion of isotonic saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamine administration should be considered. If ingestion is recent, take measures to eliminate trandolapril (e.g., administration of an absorbent and sodium sulphate). It is not known whether trandolapril (or the active metabolite, trandolaprilate) can be eliminated by 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

Category and class: A.7.1.3 Other hypotensives

Pharmacotherapeutic group: Verapamil, combinations

ATC code: C09BB10

Mechanism of action

TARKA tablets contain the pro-drug trandolapril, a non-peptide angiotensin-converting enzyme

(ACE) inhibitor with a carboxyl group but without a sulphydryl group, and verapamil, a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist).

Verapamil:

Verapamil exerts its pharmacological effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells.

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. Verapamil reduces myocardial oxygen consumption *in vitro* directly by intervening in the energy consuming metabolic processes of the myocardial cell, and indirectly by diminishing the peripheral resistance (afterload). It prolongs impulse conduction in the AV node.

2. *Reduction of myocardial contractility*

   The negative inotropic effect 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.

Spastic bronchitis and similar conditions, therefore, are not contraindications for verapamil.

Trandolapril:

Trandolapril suppresses the plasma renin angiotensin aldosterone system (RAAS) which plays a major part in regulating blood volume and blood pressure. Renin is an endogenous enzyme synthesised by the kidneys and released into the circulation where it converts angiotensinogen into angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by the

angiotensin-converting enzyme, peptidyl dipeptidase, into 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 produce 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 only small, an increase in serum potassium concentrations may occur, along with sodium and fluid loss. Inhibition of the negative feedback mechanism of angiotensin II on renin production results in increased 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 leads to increased activity of the circulating and local kalikrein-kinin system. This contributes to peripheral vasodilation by activating the prostaglandin system. This mechanism may be involved in the hypotensive effects of ACE inhibitors and is responsible for certain adverse reactions. In patients with hypertension, the administration of ACE inhibitors results in a decrease in supine and standing blood pressure to 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 begins one-hour post-dose, with a peak effect between 8 and 12 hours, and lasts for at least 24 hours but trandolapril does not interfere with the circadian blood pressure pattern.

5.2 Pharmacokinetic properties

Neither animal studies nor healthy volunteer studies could demonstrate pharmacokinetic or RAAS

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

Verapamil:

Verapamil hydrochloride is a racemic substance comprising the R and S enantiomer in equal proportions. Verapamil is extensively metabolised.

Absorption:

About 90 % of orally administered verapamil is absorbed. It is bound mainly to α_1-acid glycoprotein and albumin. Mean bioavailability is as low as 22 % because of an extensive first-pass effect in the liver and displays considerable 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:

Verapamil is widely distributed in body tissue. The distribution volume is between 1,8 and 6,8 L/kg in healthy subjects. The peak plasma concentration is reached after 4 hours on average. The peak plasma concentration of norverapamil is reached about 6 hours post-dose.
Steady state after repeated/single daily dosing is reached after 3 – 4 days. Plasma protein binding of verapamil is approximately 90 %.

Metabolism:

In healthy men, orally administered verapamil hydrochloride is largely metabolised in the liver. Twelve metabolites have been identified, most of them only in traces. The main metabolites are various N and O-dealkylated products of verapamil. Of these metabolites, only norverapamil has a noteworthy pharmacological effect (approximately 20 % of the initial binding), as observed in a

study with dogs.

Elimination:

The mean elimination half-life after repeated administration is 8 hours. 3 – 4 % of a dose is excreted unchanged, via the kidneys. Metabolite excretion is via the urine (70 %) and faeces (16 %). The total clearance of verapamil is almost as high as the liver circulation, approximately 1 L/h/kg (range: 0,7 to 1,3 L/h/kg). Norverapamil is one of 12 metabolites identified in urine. It possesses approximately 10 – 20 % of the pharmacological activity of verapamil and accounts for 6 % of the excreted medicine. The steady-state plasma concentrations of norverapamil and verapamil are similar.

Elderly patients:

Age can affect the pharmacokinetic profile of verapamil in the treatment of hypertension. The elimination half-life may be prolonged in elderly patients. The antihypertensive effect of verapamil is not age-dependent.

Impaired renal function:

The pharmacokinetic profile of verapamil does not change in patients with impaired renal function. Verapamil and norverapamil are not removed to any significant extent by haemodialysis.

Impaired hepatic function:

Bioavailability and the elimination half-life of verapamil are increased in patients with liver cirrhosis. However, the pharmacokinetic profile is not altered in patients with compensated hepatic dysfunction. Renal function has no effect on verapamil elimination.

Children and adolescents:

Only limited pharmacokinetic information in children and adolescents is available. Following intravenous administration, the mean half-life of verapamil was 9,17 hours and the mean

clearance 30 L/h compared to approximately 70 L/h for an adult weighing 70 kg.
Steady-state plasma concentrations following oral administration appear to be somewhat lower in children and adolescents compared to adults.

Trandolapril:

Absorption:

The amount absorbed is equivalent to 40 to 60 % of the administered dose and is not affected by food consumption. In normal volunteers the peak concentration of trandolapril is observed 30 minutes after administration.

Distribution and biotransformation:

Trandolapril disappears very rapidly from the plasma with a half-life of less than one hour. The peak plasma concentration of trandolaprilat is reached after 4 to 6 hours in the fasting state.
In the plasma trandolaprilat is more than 80 % protein bound. It binds saturably, with a high affinity, to converting enzyme. The major proportion of circulating trandolaprilat is also non-saturably bound to albumin. After repeated administration of trandolapril in a single daily dose steady state is reached on average in four days, both in healthy volunteers and in young or elderly hypertensives. The effective accumulation half-life of trandolaprilat is between 16 and 24 hours.

Metabolism:

Trandolapril is hydrolysed to the active component trandolaprilat, a specific angiotensin-converting enzyme (ACE) inhibitor. The amount of trandolaprilat formed is not modified by food consumption.

Elimination:

Trandolaprilat eliminated in urine in the unchanged form accounts for 10 to 15 % of the dose of trandolapril administered. After oral administration of radioactively labelled trandolapril in man,

one third of the radioactivity is recovered in the urine and two thirds are recovered in the faeces. The renal clearance of trandolaprilat shows a linear correlation with creatinine clearance.

Impaired renal function:

The trandolaprilat plasma concentrations are significantly higher in patients with a creatinine clearance less than 30 mL/min. However, after repeated dosing in patients with chronic renal failure, steady state is also reached after four days, regardless of the extent of kidney function impairment.

Impaired hepatic function:

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.

Children and adolescents:

The pharmacokinetic profile has not been investigated in children under 18 years of age.

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 render negligible any concerns for human safety. Genotoxicity assays revealed no specific hazard for humans. Animal studies have shown that ACE inhibitors tend to have negative effects on late foetal development, resulting in foetal death and congenital abnormalities of the skull in particular. Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These abnormalities are thought to be partly due to the pharmacological activity of these active substances and may be related to ACE inhibitor-induced oligohydramnios. The abnormalities may also be partly due to ischemia resulting from maternal hypotension and a decrease in foetal-placental blood flow and

oxygen/nutrient delivery to the foetus. There is no evidence of a carcinogenic potential with either trandolapril or verapamil.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients include the following:

anhydrous silica,

black ferric oxide,

docusate sodium,

hydroxypropylcellulose,

hypromellose,

lactose monohydrate,

macrogol,

magnesium stearate,

maize starch,

microcrystalline cellulose,

povidone,

red ferric oxide,

sodium alginate,

sodium,

stearyl fumarate,

talc,

titanium dioxide, and

yellow ferric oxide.

6.2 Incompatibilities

Not applicable.

Sign:

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 ˚C.

Protect from light and humidity.

6.5 Nature and contents of container

Cartons containing 28 tablets. The tablets are enclosed in colourless, transparent PVC/PVDC blister strips with an aluminium foil backing.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott Place, 219 Golf Club Terrace

Constantia Kloof

1709

South Africa

8. REGISTRATION NUMBER

TARKA 180/2: A39/7.1.3/0508

TARKA 240/4: A39/7.1.3/0547

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 October 2009

Sign:

10. DATE OF REVISION OF THE TEXT

To be allocated.

Sign: