PROFESSIONAL INFORMATION FOR MAVIK

SCHEDULING STATUS S3

1. NAME OF MEDICINE

MAVIK 0,5 mg Hard capsules

MAVIK 2 mg Hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MAVIK 0,5 mg: Each hard capsule contains 0,5 mg trandolapril.

MAVIK 2 mg: Each hard capsule contains 2 mg trandolapril.

Excipients with known effect:

MAVIK 0,5 mg: Each hard capsule contains 56,0 mg lactose monohydrate.

MAVIK 2 mg: Each hard capsule contains 55,5 mg lactose monohydrate.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

MAVIK 0,5 mg: No. 4 capsule consisting of a red body and a yellow cap, containing practically white granules.

MAVIK 2 mg: No. 4 capsule consisting of a red body and a red cap, containing practically white granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate hypertension.

4.2 Posology and method of administration

Posology

May be taken with/without meals preferably at the same time every day.

Adults: Initial dose is 0,5 mg as a single daily dose. The dose should be adjusted according to blood pressure response. The usual effective maintenance dose is 2 mg as a single daily dose with a maximum of 4 mg. If the patient is still unsatisfactory at a dose of 4 mg, combination therapy should be considered.

The full therapeutic effect may take several weeks. Therefore, if the desired effect has not been achieved within 2 to 4 weeks the dose may be increased.

Dosing in high-risk individuals:

Diuretic-treated patients

In patients who are at risk from a stimulated renin-angiotensin system (e.g. patients with water and sodium depletion), the diuretic should be discontinued two or three days before beginning therapy with 0,5 mg trandolapril to reduce the likelihood of symptomatic hypotension. The diuretic may be resumed later if required.

Elderly patients

The dose in elderly patients is the same as in non-elderly adults. There is no need to reduce the dose in elderly patients with normal renal and hepatic function. Caution should be exercised in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency.

The dose should be titrated according to the need for the control of blood pressure. In these patients, therapy should be initiated at a dose of 0,5 mg daily.

Renal impairment

A lower dose is required. If creatinine clearance is 31 – 70 mL/min (moderate renal impairment)

the usual adult dosage is recommended. The dose may be increased as needed according to therapeutic response, for patients with more severe renal impairment (creatinine clearance between 10 mL/min and 30 mL/minute), MAVIK should be initiated at a dose of 0,5 mg and increased if necessary. In patients with severe renal impairment (creatinine clearance less than 10 mL/min), the recommended daily dose is 0,5 mg, the daily maximum dose should not exceed 2 mg. In these patients, therapy should be under close medical supervision.

Renovascular hypertension

Treatment should be started in hospital under close medical supervision with low doses and careful dose titration. The patient should be monitored.

Hepatic impairment

In patients with severely impaired liver function a decrease in the metabolic clearance of the parent compound trandolapril and the active metabolite trandolaprilat results in a large increase in plasma trandolapril levels and to a lesser extent an increase in trandolaprilat levels. Treatment with MAVIK should therefore be initiated at a dose of 0,5 mg once daily under close medical supervision.

Dialysis

It is not known 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.

Method of administration

Oral administration.

4.3 Contraindications

- Hypersensitivity to trandolapril, other angiotensin-converting (ACE) inhibitors or to any of the excipients of MAVIK (see section 6.1).
- Patients with a history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Aortic stenosis.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- Concomitant use of fluoroquinolones with MAVIK is contraindicated in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in elderly patients (see sections 4.4. and 4.5).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Pregnancy and lactation (see section 4.6).
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with MAVIK may lead to toxic blood concentrations of lithium (see section 4.5).
- The concomitant use of MAVIK with aliskiren-containing products is contraindicated. (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving MAVIK, the treatment should be stopped promptly and switched to a different class of antihypersensitive medicine (see sections 4.3

and 4.6).

Kidney function must be checked prior to using MAVIK.

Particularly at the start of therapy, it should only be administered with intensive monitoring of blood pressure and/or representative laboratory parameters in patients:

- with salt deficiency and/or dehydration
- with impaired kidney function
- with severe hypertension
- over 65 years old
- with concurrent cardiac insufficiency.

Liver function disorder

As trandolapril as a prodrug, is first metabolised in the liver to the active substance, in patients with impaired liver function, caution is particularly required, and close monitoring indicated.

Symptomatic hypotension

Under certain conditions there may occasionally be a symptomatic hypotension at the start of administration or on increasing the dose, in patients with dehydration or salt deficiency because of a long-term administration of diuretics, sodium-reducing diet, dialysis, after diarrhoea or vomiting.

In these patients before treatment starts the diuretic administration should be discontinued and/or dehydration or salt deficiency balanced.

In patients with ischaemic cardiac disease or cerebrovascular disease, in which excessive fall in blood pressure may lead to myocardial infarction or cerebrovascular event, close monitoring during the start of treatment and on adjustment of the dose is necessary.

Agranulocytosis and marrow depression

Agranulocytosis and bone marrow depression was observed during ACE inhibitor treatment. These reactions occur more frequently in patients with a certain restriction of kidney function, if this is accompanied by collagenosis.

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.

Diabetes mellitus

Increased risk of hyperkalaemia, as well as hypoglycaemia may occur.

Hypersensitivity or angioedema

During treatment with trandolapril, as in MAVIK, angioedema with swelling of the face, extremities, tongue and glottis and/or the entire larynx may occur. A higher rate of angioedema has been found in dark-skinned patients than in light-skinned patients.

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

During treatment with ACE inhibitors intestinal angioedema has also been reported. This should be taken into consideration in patients who report abdominal pain (with or without nausea or vomiting) during treatment with MAVIK.

Patients with angioedema must discontinue MAVIK immediately and are monitored until the oedema disappears.

Oedema that only occurs in the face normally disappears spontaneously. However, if the oedema extends to the glottis, because of the narrowing of the airways there is a danger to life.

In case of angioedema with tongue, glottis or larynx involvement, the immediate subcutaneous administration of 0,3 – 0,5 mL epinephrine (adrenalin) solution (1:1 000) as well as corresponding further suitable therapeutic measures are necessary.

MAVIK is contraindicated if the angioedema has already occurred as a side effect of an ACE inhibitor (see also section 4.3).

Patients with renovascular hypertension

While curative treatment of the renovascular hypertension has not begun, or if such treatment is not considered, the use of ACE inhibitors, such as MAVIK, may be indicated.

The risk of severe arterial hypotension and renal insufficiency is increased in patients treated with ACE inhibitors with unilateral or bilateral renal artery stenosis.

Diuretics may further increase the risk. The loss of renal function may only be accompanied by slight changes in serum creatinine, even in patients with unilateral renal artery stenosis. In these patients the start of treatment should be closely medically monitored with low dose and cautious dose adjustment as an in-patient. Diuretic administration should be terminated and the renal function and serum potassium should be monitored during the initial weeks of treatment.

Note

In some patients during diuretic administration, if this treatment was only recently started, there may be an excessive drop in blood pressure after treatment with MAVIK begins.

Impairment of renal function

An acute deterioration in renal function (acute renal failure) may particularly in patients with existing impairment of renal function, manifest cardiac insufficiency or renal artery stenosis (bilateral, or unilateral if only one kidney is present) as well as after kidney transplant. In some patients with high blood pressure or identifiable existing kidney disease, trandolapril may result in increased blood-urea nitrogen and serum creatinine levels when administered concomitantly with diuretics. Proteinuria may also occur.

In patients with renal insufficiency the risk of hyperkalaemia should be considered, and the patient's electrolyte balance regularly checked.

Fluoroquinolones and MAVIK

Concomitant use of fluoroquinolones and MAVIK may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see sections 4.3 and 4.5). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or MAVIK whether used separately and/or concomitantly.

Serum potassium

ACE inhibitors, as in MAVIK, may trigger hyperkalaemia since they prevent aldosterone release. The effect is generally insignificant in patients with normal kidney function. However, patients with renal impairment and/or those who are taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or cotrimoxazole (also known as trimethoprim/ sulfamethoxazole) and aldosterone antagonists or angiotensin receptor blockers, may develop hyperkalaemia. Caution should be exercised when administering potassium-sparing diuretics and angiotensin receptor blockers to patients taking MAVIK. Serum potassium levels and kidney function should be monitored (see section 4.5).

Surgical patients/anaesthesia

In patients who have to undergo major surgery or general anaesthesia with anaesthetics that may cause hypotension, MAVIK following compensatory renin secretion may inhibit the formation of angiotensin II.

Children

Safety and efficacy have not been investigated in children.

Cough

During treatment with an ACE inhibitor, such as MAVIK, a dry and non-productive cough may develop which disappears after discontinuation of MAVIK.

Anaphylactoid and similar reactions

If emergency dialysis or haemofiltration with poly (acrylonitrile, sodium 2 methallyl sulfonate) high flux membranes (e.g. "AN 69") is required during therapy with MAVIK, there is the risk of anaphylactoid reactions, including even life-threatening shock conditions.

LDL apheresis:

Life-threatening anaphylactoid reactions have been noted when patients on LDL apheresis take ACE inhibitors, such as MAVIK, at the same time (see section 4.3).

Desensitisation:

Anaphylactoid reactions (in some cases life threatening) may occur in patients receiving ACE inhibitor therapy and concomitant desensitisation against animal venoms.
Therefore, do not use MAVIK during LDL apheresis with dextran sulphate or during desensitisation therapy with insect poison.

Dual renin angiotensin aldosterone system blockade (RAAS)

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor

antagonists or aliskiren increases the risk of hypotension, hyperkalaemia and a reduction in renal function (including acute renal failure). Dual blockade of RAAS through the combined use of MAVIK and aliskiren is therefore contraindicated (see section 4.3). MAVIK should not be used concomitantly with aliskiren (see section 4.3).

If treatment with dual blockade is considered necessary, this should only take place under supervision by a specialist and while carrying out close monitoring of renal function, electrolyte levels and blood pressure.

ACE inhibitors, such as MAVIK and angiotensin II receptor antagonists should not be used concomitantly in patients with diabetic nephropathy.

Pregnancy

ACE inhibitors, such as MAVIK, should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative blood-pressure-lowering treatments which have an established safety profile for use in pregnancy. When pregnancy has been established, treatment with MAVIK must be stopped immediately, and, if appropriate, alternative therapy should be initiated (see sections 4.3 and 4.6).

Lactose monohydrate

MAVIK contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, total lactase deficiency or glucose-galactose malabsorption should not take MAVIK.

Sodium

MAVIK contains less than 1 mmol (23 mg) sodium per hard capsule, that is to say essentially “sodium-free”.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of MAVIK with:

- Table salt: Reduces MAVIK's capacity to lower blood pressure and improve symptoms of weak cardiac output.
- Antihypertensives: Concomitant use of diuretics or other antihypertensives may potentiate the blood-pressure-lowering effect of MAVIK. Adrenoreceptor antagonists should only be combined with MAVIK with careful monitoring.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) and COX2 inhibitors: As with all antihypertensives, the administration of nonsteroidal anti-inflammatory drugs (including acetylsalicylic acid when using a higher dose as an anti-inflammatory medicine, e.g. for pain relief) may reduce the antihypertensive effects of MAVIK. Possible reduction in MAVIK's capacity of lowering blood pressure and of improving symptoms of weak cardiac output. Blood pressure monitoring should be increased when any NSAID and/or COX2 inhibitor is added or discontinued in a patient treated with MAVIK.
- Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes: although serum potassium levels generally stay within the normal range, hyperkalaemia may occur in some patients treated with trandolapril. Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes may lead to a significant rise in serum potassium levels. Caution should also be exercised if MAVIK is administered concomitantly with other medicines that increase serum potassium levels such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxaxole) because trimethoprim is known to act as a potassium-sparing diuretic such as amiloride. Combination therapy comprising MAVIK and the afore-mentioned medicines is therefore not recommended. If concomitant administration is indicated, proceed with caution and monitor serum potassium levels on a regular basis. This applies to patients with renal failure, diabetes mellitus and/or left ventricular dysfunction after myocardial infarction. MAVIK can delay the potassium loss caused by thiazide-type diuretics.
- Ciclosporin: concomitant administration of MAVIK and ciclosporin may trigger hyperkalaemia. Serum potassium levels should be monitored.

- Heparin: concomitant administration of MAVIK and heparin may trigger hyperkalaemia. Serum potassium levels should be monitored.
- Antacids: Decrease in bioavailability of ACE inhibitors.
- Lithium: Increases in lithium concentrations have been reported. Frequent monitoring of serum lithium concentrations is recommended.
- Alcohol: Increase in bioavailability of ACE inhibitors. Alcohol also increases the risk of hypotension.
- Concomitant use of antidiabetic medicines (insulin or oral hypoglycaemic medicines) may cause an increased blood glucose lowering effect with greater risk of hypoglycaemia. In such cases, a dose adjustment of the blood-sugar-lowering medicine or dose of this medicine may be required.
- Concomitant treatment with neuroleptics or tricyclic antidepressants may increase the risk of orthostatic hypotension.
- Medicines that increase the risk of angioedema: concomitant administration of MAVIK and sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.4).
- Concomitant administration of MAVIK and racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may increase the risk of angioedema (see section 4.4).
- Anaphylactoid reactions to high-flux polyacrylonitrile membranes used in haemodialysis have been reported in patients treated with ACE inhibitors. This combination should be avoided when prescribing ACE inhibitors, such as MAVIK to renal dialysis patients.
- Hypnotics, narcotics, anaesthetics: Incremental drop in blood pressure (inform anaesthesiologist about the therapy with MAVIK).
- Sympathomimetics: Adverse impact on the blood-pressure-lowering effect of ACE inhibitors, as in MAVIK. To check whether the desired effect has been achieved, the patients should be carefully monitored.
- Allopurinol, cytostatic or immunosuppressive medicines or systemic corticosteroids,

procainamide: Decrease in leukocyte count in the blood, may increase the risk of leucopenia, if used concomitantly.

- Cimetidine: No significant interaction has been found between trandolapril, as in MAVIK and cimetidine.
- Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor, such as MAVIK therapy.
- Dual blockade of the RAAS with ARBs, ACE inhibitors, 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 (see sections 4.3 and 4.4).
- Fluoroquinolones: Concomitant use of fluoroquinolones and MAVIK may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see sections 4.3 and 4.4).
- No interaction upon concomitant administration of MAVIK with thrombolytics, aspirin, beta blockers, calcium antagonists, nitrates, anticoagulants or digoxin was observed in patients with left ventricular dysfunction after myocardial infarction.

Children

Interaction studies have only been carried out in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of MAVIK is contraindicated during pregnancy.

Pregnant women should be informed of the potential hazards to the fetus and must not take

MAVIK during pregnancy (see section 4.3). 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 MAVIK should be stopped immediately and if appropriate, alternative therapy should be started.

Fetal exposure to ACE inhibitors, such as MAVIK, during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spina bifida) and of kidney malformations.

MAVIK passes through the placenta and can be presumed to cause disturbance in fetal blood pressure regulatory mechanisms.

Oligohydramnios as well as hypotension, oliguria and anuria in new-borns, have been reported after administration of MAVIK during the second and third trimester. Cases of defective skull ossification have been observed.
Prematurity and low birth mass can occur (see section 4.3).

Breastfeeding

Safety in lactation has not been established (see section 4.3).

4.7 Effects on ability to drive and use machines

MAVIK may cause drowsiness, dizziness, fatigue or blurred vision (see section 4.8) which may affect the ability to drive a vehicle and use machines. Caution is advised before performing tasks requiring alertness until the effects of MAVIK are known.

4.8 Undesirable effects

The following table lists the undesirable effects that have been reported in clinical trials with

trandolapril (Hypertension trials [n = 2 520] and post-myocardial infarction trials [n = 876] and from post-marketing observations.

The undesirable effects, which are assessed as at least possible on taking trandolapril, are classified under the corresponding organ system and listed by frequency, according to the following convention: Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1 000 to < 1/100), Rare (≥ 1/10 000 to < 1/1 000) and Not known (frequency cannot be estimated from the available data).

Within each frequency group undesirable effects are shown in order of decreasing severity (if the degree of severity can be assessed).

MedDRA system organ class	**common**	**uncommon**	**rare**	**very rare**	**not known**
Infections and infestations		Infection of the upper respiratory tract	Urinary tract infection, Bronchitis, Pharyngitis		Sinusitis*, Rhinitis*, Glossitis*
Blood and lymphatic system disorders			Leucopenia, Anaemia*, Thrombocyte formation disorders, Leukocytopoietic disorders		Agranulocytosis, Pancytopenia*, Thrombocytopenia, Haemolytic anaemia*
Immune system disorders			Allergic hypersensitivity reactions including pruritus and rash		
Metabolism and nutrition disorders			Hyperglycaemia, Hyponatraemia*, Hypercholesterinaemia, Hyperlipidaemia, Hyperuricaemia,		Hyperkalaemia

			Gout, Anorexia, Increased appetite, Enzyme changes		
Psychiatric disorders		Insomnia, Reduced libido	Hallucinations, Depression, Sleep disorders*, Anxiety, Agitation, Apathy		Mental confusion*, Mood alterations*
Nervous system disorders	Headache, Dizziness	Drowsiness	Cerebrovascular event, Syncope, Myoclonus, Paraesthesia*, Migraine, Migraine without aura, Changes in taste		Transient ischaemic attacks*, Cerebral haemorrhage*, Balance disorder
Eye disorders			Inflammation of eye lids, Conjunctive oedema, Vision disorders, Eye disorders		Blurred vision*
Ear and labyrinth disorders		Vertigo*	Tinnitus		
Cardiac disorders		Palpitations	Myocardial infarction*, Myocardial ischaemia, Angina pectoris*, Cardiac insufficiency, Ventricular tachycardia, Tachycardia*,		AV block*, Cardiac arrest*, Arrhythmia

			Bradycardia*		
Vascular disorders	Hypotension*	Hot flushes	Hypertension, Angiopathy, Orthostatic hypotension, Peripheral vascular disease, Venous varicosis		
Respiratory, thoracic and mediastinal disorders	Cough	Inflammation of the upper respiratory tract, Congestion of the upper respiratory tract	Dyspnoea, Nosebleeds, Inflammation of the pharyngeal mucosa, Laryngeal pain, Productive cough, Respiratory tract disorders (general)		Bronchospasm*
Gastrointestinal disorders		Nausea, Diarrhoea, Non-specified gastrointestinal complaints, Constipation, Gastrointestinal disease (general)	Haematemesis, Gastritis, Abdominal pain, Vomiting, Dyspepsia, Dry mouth, Flatulence		Ileus, Pancreatitis, Intestinal oedema*, Indigestion*
Hepatobiliary disorders			Hepatitis (hepatocellular or cholestatic)*	Cholestasis	Jaundice*, Abnormal liver function tests, Increased transaminase
Skin and subcutaneous tissue disorders		Pruritus, Rash, Exanthema	Facial oedema, Psoriasis*, Hyperhidrosis, Eczema, Acne, Dry skin,	Dermatitis	Angioedema, Alopecia, Urticaria*, Severe skin disorders including pemphigus*,

			Skin disorders (general)		Stevens-Johnson syndrome*, toxic epidermal necrolysis*, erythema multiforme*, Photosensitivity* or other dermatological manifestations
Musculoskeletal and connective tissue disorders		Backache, Muscle spasms, Pain in the extremities	Arthralgia, Bone pain, Osteoarthritis		Myalgia*
Renal and urinary disorders			Renal insufficiency, Azotaemia, Polyuria, Pollakiuria		
Reproductive system and breast disorders		Erectile dysfunction			Uraemia*, Oliguria*, Anuria*, Renal dysfunction*, Acute renal failure*
Congenital, familial and genetic disorders			Congenital arterial deformities, Ichthyosis		
General disorders and administration site conditions	Asthenia	Malaise, Chest pain, Peripheral oedema, Abnormal feeling	Oedema, Fatigue		Pyrexia
Investigations			Hyperbilirubinaemia*	Increased: gamma-GT, lipase, immunoglobulin	Decreased: thrombocytes, haemoglobin*, haematocrit*,

					Increased: serum creatinine in the blood, urea in the blood, GOT, GPT, liver enzymes, alkaline phosphatase in the blood, lactate dehydrogenase in the blood, Abnormal laboratory test results, ECG
Injury, poisoning and procedural complications			Injury		

*Indicates undesirable effect of the active substance class.

Other

A symptom complex has been reported which may include vasculitis, myalgia, arthritis/arthralgia, a positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis.

Notes

The above-mentioned laboratory parameters should be monitored prior to and regularly during treatment.

Particularly at the start of treatment and in at-risk patients (patients with renal insufficiency, collagen diseases, treatment with immunosuppressants, cytostatic medicines, allopurinol, procainamide), monitoring of serum electrolyte and creatinine concentrations as well as blood count are advised in the short term.

Should symptoms such as fever, lymph node swelling and/or a sore throat occur during treatment, the white blood cell count must be evaluated immediately.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms of overdose

The highest doses of trandolapril used in clinical trials were 32 mg as a single dose for healthy subjects and 16 mg as repeat daily doses administered to hypertensive patients. It was tolerated without symptoms of an overdose.

Depending on the extent of overdosing with ACE inhibitors, the following symptoms expected with ACE inhibitors are severe hypotension, shock, stupor, bradycardia, circulatory shock, electrolyte disturbance and renal failure.

Treatment of overdose

Treatment is symptomatic and supportive. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. Treatment consists of volume expansion to correct hypotension and treating dehydration and electrolyte imbalances. It is not known for certain if trandolapril or trandolaprilat are removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3 Other hypotensives

Pharmacotherapeutic group: ACE inhibitor

ATC code: C09AA10

MAVIK capsules contain the prodrug, trandolapril, a non-peptide angiotensin converting enzyme (ACE) inhibitor with a carboxyl group but without a sulfhydryl group. Trandolapril is absorbed and then non-specifically hydrolysed to its, long-acting active metabolite, trandolaprilat.

Trandolaprilat inhibits angiotensin I-converting enzyme (ACE) activity. It inhibits the conversion of the relatively inactive angiotensin I to the active angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone. Decreased angiotensin II levels result in a decrease in vasopressor activity and a reduction in aldosterone secretion, which may result in small increases in serum potassium.

It is also thought that ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

Due to the strong inhibition of ACE even in low concentrations, trandolapril reduces the formation of angiotensin II. It leads to a reduction in aldosterone secretion and an increase in plasma renin activity due to the suppression of negative feedback. It therefore intervenes in the renin angiotensin aldosterone system, which plays a crucial role in regulating blood volume and blood pressure.

Other mechanisms that may be related to vasodilatory activities of the ACE inhibitors involve blocking of bradykinin decomposition and release of prostaglandins as well as reduction in sympathetic nervous system activity. These combined properties might also explain the observed findings of a remission in cardiac hypertrophy and improvement in vessel elasticity in humans.

In patients with hypertension, trandolapril leads to a reduction in systolic and diastolic blood pressure. This antihypertensive effect is maintained even at low plasma renin levels.

The reduction in peripheral resistance induced by trandolapril is neither accompanied by retention of fluids and sodium nor by tachycardia.

The antihypertensive effect of trandolapril sets in about one hour after administration, the maximum effect is usually reached after 4 – 6 hours. The effect lasts for at least 24 hours without changing the circadian blood pressure rhythm.

The blood pressure lowering effect is maintained in long-term therapy without development of tolerance. No rebound effect occurs when trandolapril is discontinued.

The combination with a diuretic or a calcium antagonist may increase trandolapril's blood pressure lowering effect.

5.2 Pharmacokinetic properties

Following oral administration, the peak plasma concentrations of trandolapril are achieved in about 1 hour after administration. The absolute bioavailability of trandolapril is about 10 %.

Trandolapril is hydrolysed to the active diacid metabolite trandolaprilat. The peak plasma concentration of trandolaprilat is reached after four to ten hours. The absolute bioavailability of trandolaprilat following trandolapril dose is about 70 %. Food does not affect the C_{max} or AUC of trandolaprilat.

Serum protein binding of trandolapril is about 80 %, and is independent of concentration. The volume of distribution of trandolapril is about 18 L. Binding of trandolaprilat is concentration-dependent, varying from 65 % at 1 000 ng/mL to 94 % at 0,1 ng/mL, indicating saturation of binding with increasing concentration.

In healthy volunteers, trandolapril has a half-life of less than one hour.

During multiple dosing of trandolapril, the steady state is reached in about four days, both in healthy volunteers and in young or elderly hypertensive patients. At steady state, the effective half-life of trandolaprilat is between 16 and 24 hours, involving a small fraction of administered drug, probably representing binding to plasma and tissue ACE.

After oral administration of the radioactive labelled product in man, 33 % of the radioactivity is found in the urine and 66 % in the faeces. About 10 – 15 % of an administered trandolapril dose is excreted as trandolaprilat in urine. A negligible amount of trandolapril is excreted unchanged in the urine (0,5 %).

Special patient populations:

Paediatric: Trandolapril pharmacokinetics have not been evaluated in patients less than 18 years of age.

Geriatric and gender: The plasma concentration of trandolapril is increased in elderly hypertensive patients, but the plasma concentration of trandolaprilat and inhibition of ACE activity are similar in elderly and young hypertensive patients. The pharmacokinetics of trandolapril and trandolaprilat and inhibition of ACE activity are similar in male and female elderly hypertensive patients.

Race: Pharmacokinetic differences have not been evaluated in different races.

Renal insufficiency: Compared to normal subjects, the plasma concentrations of trandolapril and trandolaprilat are approximately two-fold greater and renal clearance is reduced by about 85 % in patients with creatinine clearance below 30 mL/min and in patients on haemodialysis. Dosage adjustment is recommended in renally impaired patients.

Hepatic insufficiency: Following oral administration in patients with mild to moderate alcoholic cirrhosis, plasma concentrations of trandolapril and trandolaprilat were, respectively, nine-fold and two-fold greater than in normal subjects, but inhibition of ACE activity was not affected. Lower doses should be considered in patients with hepatic insufficiency.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Lactose monohydrate

Povidone (Type K25)

Sodium stearyl fumarate.

Capsules shell:

Gelatine

Titanium dioxide (E171)

Sodium laurilsulfate.

Colourants:

Iron oxide yellow (E172)

Erythrosine (E127).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

MAVIK 0,5 mg: 24 months

MAVIK 2 mg: 36 months

6.4 Special precautions for storage

Store in a dry place, at or below 25 °C.

Store the capsules in the outer carton until required for use.

6.5 Nature and contents of container

Pack of 30 capsules. Capsules are enclosed in PVC blister strips, with aluminium foil backing.

6.6 Special precautions for disposal

No special requirements.

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(S)

MAVIK 0,5 mg: 28/7.1.3/0261

MAVIK 2 mg: 28/7.1.3/0263

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

MAVIK 0,5 mg: 29 December 1993

MAVIK 2 mg: 29 December 1993

10. DATE OF REVISION OF TEXT

MAVIK 0,5 mg: 27 November 2023

MAVIK 2 mg: 27 November 2023

NAME AND ADDRESS OF MANUFACTURER

AbbVie Ireland NL B.V.

Manorhamilton Road

Sligo

Ireland

Country	**Product**	**Pack size**	**Registration number**	**Scheduling status**
Mauritius	MAVIK 0,5 mg	28	Not Retained	Prescription
	MAVIK 2 mg	28	Not Retained	Prescription
Namibia	MAVIK 0,5 mg	TBC	04/7.1.3/1274	NS2
	MAVIK 2 mg	TBC	04/7.1.3/1275	NS2