PACKAGE INSERT FOR MAVIK

SCHEDULING STATUS S3

PROPRIETARY NAME AND DOSAGE FORM

MAVIK 0,5 mg Capsules
MAVIK 2 mg Capsules
MAVIK 4 mg Capsules

COMPOSITION

MAVIK 0,5 mg : Each capsule contains 0,5 mg trandolapril
MAVIK 2 mg : Each capsule contains 2 mg trandolapril
MAVIK 4 mg : Each capsule contains 4 mg trandolapril

Contains lactose (lactose monohydrate)

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION
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 hydrolyzed 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.

Pharmacokinetics :
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 hydrolyzed 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 1000 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 labeled 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:

Pediatric: 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 hemodialysis. 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.

INDICATIONS

Mild to moderate hypertension.

CONTRA-INDICATIONS

- Sensitivity to any of the components of **MAVIK**.
- Patients with a history of angioedema related to previous ACE-inhibitor therapy or angiotensin receptor blocker.
- Hereditary or idiopathic angioedema.
- Aortic stenosis
- Hypertrophic obstructive cardiomyopathy
- Renal artery stenosis in patients with a single kidney.
- Pregnancy
- Lactation
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride
- Porphyria

WARNINGS

Should a woman become pregnant while receiving an ACE inhibitor, the treatment must be stopped promptly and changed to a different medicine. (SEE PREGNANCY AND LACTATION).

Should a woman contemplate pregnancy, the doctor should consider alternative medication (SEE PREGNANCY AND LACTATION).

MAVIK should be used with caution in the following conditions :

- Cerebrovascular disease or ischaemic heart disease – Reduction in blood pressure could aggravate these conditions and may result in myocardial infarction and cerebro- vascular accidents.
- 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.
- Volume depleted patients (e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting). Although it may occur in normo volumic patients, hypotension is more likely in volume depleted patients. A sudden reduction in angiotensin II may result in sudden and severe hypotension. There is also an increased risk of **MAVIK** induced renal failure, especially in those with congestive heart failure.
- Patients at a high risk of symptomatic hypotension, e.g. patients with salt or volume depletion with or without hyponatremia should have these conditions corrected before therapy with **MAVIK**. Monitoring is required after initiating therapy.
- Severe autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma increase the risk for development of neutropenia or agranulocytosis.
- In acute myocardial infarction, treatment with **MAVIK** should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 micromol/l or proteinuria exceeding 500 mg/24 hours).

  If renal dysfunction develops during treatment (serum creatinine concentrations

exceeding 177 micromol/l or doubling of the pre-treatment value) then **MAVIK** may need to be withdrawn (**see also Contra-indications)**.

- In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function

- Hypotension in acute myocardial infarction: Treatment with **MAVIK** must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These include patients with systolic blood pressure of 13.33 kPa or lower or cardiogenic shock. During the first three days following the infarction, the dose should be reduced if the systolic blood pressure is 15.99 kPa or lower. Maintenance doses should be reduced to 0.5 mg if systolic blood pressure is 13.33 kPa or lower. If hypotension persists (systolic blood pressure less than 11.99 kPa or more than 1 hour) then **MAVIK** should be withdrawn.

- Bone marrow depression: Increased risk of agranulocytosis and neutropenia.

- Diabetes mellitus: Increased risk of hyperkalaemia, as well as hypoglycaemia may occur.

- Hyperkalaemia: **MAVIK** may cause an increase in serum potassium levels.

- Renovascular disease: **MAVIK** should not be used in patients with renovascular disease or suspected renovascular disease, but it may be used cautiously in severe resistant hypertension in such patients. In this instance, **MAVIK** should only be used under specialist supervision. The elderly, patients with peripheral vascular diseases or generalized atherosclerosis may have asymptomatic renovascular disease. (SEE DOSAGE AND DIRECTIONS).

- Renal artery stenosis, bilateral or in one kidney or renal transplant: Increased risk of renal function impairment may increase blood urea and serum creatinine concentrations, which may be reversible upon discontinuation of therapy. There is also an increased risk of agranulocytosis and neutropenia when immunosuppressants are concurrently administered.

- Renal function impairment: Decreased elimination of **MAVIK** resulting in an increased risk of hyperkalaemia. These patients may require lower doses.

- Anaphylactoid reactions have occurred in patients using ACE inhibitors during desensitising protocols involving for example, hymenoptera venom.

- Anaphylactoid reactions have been reported in patients exposed to either high-flux membrane dialysis or low-density lipoprotein apheresis with dextran sulfate absorption.

- Hypersensitivity / Angioedema: If angioedema of the face, extremities, lips, tongue, glottis and/or larynx is observed in patients with **MAVIK**, **MAVIK** should be discontinued promptly. These patients should be monitored to ensure complete resolution of symptoms.

- Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate emergency therapy should be administered. This may include the administration of adrenaline and/or the maintenance of a patient airway.

  The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred. **These patients should never receive ACE inhibitor therapy again.**

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

- Porphyria

- Safety and efficacy in children has not been established.

- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride may lead to hyperkalaemia, which may be severe and lead to cardiac conduction abnormalities, dysrrythmias and cardiac arrest (refer to "CONTRA-INDICATIONS")

INTERACTIONS

Concomitant use of **MAVIK** with:

- Diuretics, alcohol and hypotension-producing medications: The antihypertensive effect is additive. Dosage adjustments may be necessary during concurrent use or when one medicine is discontinued. Adrenergic-blocking drugs should only be combined with trandolapril under careful supervision.

- Loop, thiazide or related diuretics: "First dose hypotension" may occur (SEE DOSAGE AND DIRECTIONS FOR USE)

- As with all antihypertensives, non-steroidal anti-inflammatory medicines (NSAIDs) may reduce the antihypertensive effects of **MAVIK**. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with **MAVIK**.

- Potassium supplements or potassium sparing diuretics such as spironolactone, triamterene or amiloride: may increase the risk of hyperkalemia, particularly in renal failure. Trandolapril may attenuate the potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly.

- Lithium: Increases in lithium concentrations have been reported. Frequent monitoring of serum lithium concentrations is recommended.

- Concomitant use of antidiabetic medicines (insulin or oral hypoglycemic agents) may cause an increased blood glucose lowering effect with greater risk of hypoglycemia.

- Anaphylactoid reactions to high-flux polyacrylonitrile membranes used in

hemodialysis have been reported in patients treated with ACE inhibitors. This combination should be avoided when prescribing ACE inhibitors to renal dialysis patients.

- The hypotensive effects of certain inhalation anesthetics may be enhanced by ACE inhibitors.

- Cytostatic or immunosuppressive agents or systemic corticosteroids may increase the risk of leucopenia, if used concomitantly.

PREGNANCY AND LACTATION

MAVIK is contraindicated in pregnancy.

Foetal exposure to ACE inhibitors during the second and third trimester can cause hypotension, renal failure, anuria, skull hypoplasia, hyperkalaemia and oliguria. Oligohydramnios may occur resulting in pulmonary hypoplasia, limb contractures and craniofacial deformation.

Infants who have been exposed in utero to **MAVIK** should be closely monitored.

It is not known if peritoneal dialysis may be of benefit in the clearance of **MAVIK** from the neonatal circulation.

Safety in lactation has not been established (see CONTRA-INDICATIONS).

DOSAGE AND DIRECTIONS FOR USE

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 4mg **MAVIK**, 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: 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.

SIDE EFFECT AND SPECIAL PRECAUTIONS

Side effects :

The following adverse reactions have been reported in long-term clinical trials with **MAVIK**. The events are displayed by system organ class and frequency, using the following convention: common (> 1/100, < 1/10), uncommon (> 1/1000, < 1/100)

System Organ Class	Frequency	Adverse Event
Nervous System disorders	Common	Headache Dizziness
Cardiac disorders	Uncommon	Palpitations
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Uncommon	Nausea
Skin and subcutaneous tissue disorders	Uncommon	Pruritus Rash
General disorders and administration site conditions	Common Uncommon	Asthenia Malaise

Reactions from Postmarketing Surveillance or Phase IV Clinical Trials
Significant adverse events seen with **MAVIK** are listed below by body system:

System Organ Class	***Frequency***	***Adverse Event***
Infections and infestations	Unknown	Bronchitis
Blood and lymphatic system disorders	Unknown	Agranulocytosis, Leucopenia
Immune system disorders	Unknown	Allergic hypersensitivity reactions including pruritus and rash
Metabolism and nutrition disorders	Unknown	Hyperkalaemia
Vascular disorders	Unknown	Orthostatic effects (including hypotension)
Respiratory, thoracic and mediastinal disorders	Unknown	Dyspnoea
Gastrointestinal disorders	Unknown	Nausea, vomiting, abdominal pain, diarrhoea, dry mouth, pancreatitis
Skin and subcutaneous tissue disorders	Unknown	Angioedema, alopecia, sweating
General disorders and administration site conditions	Unknown	Fever
Investigations	Unknown	Increases in urea and serum creatinine, decreased platelets, elevated liver enzymes (including ALT and AST).

The following adverse events have been reported with ACE inhibitors as a class and may also occur with MAVIK:

Blood and lymphatic system disorders

Pancytopenia, hemolytic anaemia, anaemia

Metabolism and nutrition disorders

Hyponatraemia

Nervous system disorders

Transient ischemic attacks, mood alterations, mental confusion, paraesthesia, vertigo, sleep disturbances

Cardiac disorders

Angina pectoris, myocardial infarction, AV block, bradycardia, cardiac arrest, tachycardia

Vascular disorders

Cerebral haemorrhage

Respiratory

Bronchospasm, rhinitis, sinusitis

Gastrointestinal disorders

Indigestion, taste disturbances

Liver/hepatic

Hepatitis (hepatocellular or cholestatic) jaundice, increases in serum bilirubin

Skin and subcutaneous tissue disorders

Urticaria, psoriasis, severe skin disorders including pemphigus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis; photosensitivity or other dermatological manifestations may occur.

Musculoskeletal and connective tissue disorders

Myalgia

Kidney/Genitourinary:

Uraemia, oliguria, anuria, renal dysfunction, acute renal failure, impotence

Investigations
Decreased hemoglobin, decreased hematocrit

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.

Special precautions :

- Myocardial infarction and cerebrovascular accidents may be due to severe falls in blood pressure in high-risk patients e.g. those with ischaemic heart disease or cerebrovascular disease.

- In volume depleted patients or patients with ischaemic heart disease or cerebrovascular disease, therapy should be monitored especially when the dose of **MAVIK** or diuretic is adjusted. If hypotension occurs, the patient should be placed in the supine position and if necessary receive an intravenous infusion of 0.9% saline.

- Increases in blood urea and serum creatinine have been seen in patients with no apparent pre-existing vascular disease, especially when **MAVIK** has been given concomitantly with a diuretic. Dosage reduction or discontinuation of **MAVIK** or the diuretic may be required.

- Signs of facial or extremity swelling or difficulty in swallowing or breathing, require immediate medical attention, because of the risk of angioedema.

- Caution when driving or performing tasks requiring alertness because of possible dizziness.

- In patients undergoing major surgery or during anaesthesia with agents that produce, **MAVIK** may block angiotensin II formation secondary to complementary renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See SIDE EFFECTS AND SPECIAL PRECAUTIONS)

Symptoms of overdose :

Symptoms expected with ACE inhibitors are severe hypotension, shock, stupor, bradycardia, 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.

IDENTIFICATION

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

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

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

PRESENTATION

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

STORAGE INSTRUCTIONS

Store in a dry place, below 25 °C.
Store the capsules in the outer carton until required for use.
Keep out of reach of children.

REGISTRATION NUMBER

MAVIK 0,5 mg	**:**	28/7.1.3/0261
MAVIK 2 mg	**:**	28/7.1.3/0263
MAVIK 4 mg	**:**	A39/7.1.3/0531

NAME AND BUSINESS ADDRESS OF APPLICANT

Abbott Laboratories S.A. (Pty) Limited
Abbott Place
219 Golf Club Terrace
CONSTANTIA KLOOF
1709
South Africa

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