PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

NATRAPRESS 5 mg Tablets

NATRAPRESS 10 mg Tablets

NATRAPRESS 20 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each NATRAPRESS 5 mg tablet contains 5 mg enalapril maleate.

Each NATRAPRESS 10 mg tablet contains 10 mg enalapril maleate.

Each NATRAPRESS 20 mg tablet contains 20 mg enalapril maleate.

Contains sugar:

NATRAPRESS 5 mg tablet – 128,808 mg lactose monohydrate per tablet.

NATRAPRESS 10 mg tablet – 126,07 mg lactose monohydrate per tablet.

NATRAPRESS 20 mg tablet – 121,81 mg lactose monohydrate per tablet.

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

NATRAPRESS 5 mg: White coloured barrel shaped uncoated tablet debossed with “5” on one side and plain on the other side.

NATRAPRESS 10 mg: Pink coloured barrel shaped uncoated tablet debossed with “10” on one side and plain on the other side.

NATRAPRESS 20 mg: Peach coloured barrel shaped uncoated tablet debossed with “20” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypertension.

Treatment of heart failure: NATRAPRESS is indicated for the treatment of symptomatic congestive heart failure, in combination with diuretics and when appropriate digitalis. In these patients NATRAPRESS improves symptoms, increases survival, and decreases the frequency of hospitalisation.

Asymptomatic left ventricular dysfunction: In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction ≤ 35 %), NATRAPRESS may decrease the rate of development of overt heart failure and may decrease the incidence of hospitalisation for heart failure.

4.2 Posology and method of administration

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

Treatment for hypertension

Adults:

The initial dose is 10 to 20 mg depending on the degree of hypertension and is given once daily. In mild hypertension the recommended initial dose is 10 mg daily. For other degrees of hypertension, the initial dose is 20 mg daily. The usual maintenance dose is one 20 mg tablet taken once daily. The dosage should be adjusted according to the needs of the patient.

Concomitant diuretic therapy in hypertension

Symptomatic hypotension may occur following the initial dose of NATRAPRESS; this is more likely in patients who are being treated currently with diuretics. Caution is recommended, therefore, since these patients may be volume or salt depleted.

The diuretic therapy should be discontinued for 2 - 3 days prior to initiation of therapy with NATRAPRESS. If this is not possible, the initial dose of NATRAPRESS should be low (5 mg

or less) to determine the initial effect on the blood pressure. Dosage should then be adjusted according to the needs of the patient. (see section 4.4).

Dosage in renal impairment:

Generally the intervals between the administration of NATRAPRESS should be prolonged and/or the dosage reduced.

Renal status	**Creatinine Clearance (mL/min)**	**Initial Dose (mg/day)**
Mild impairment	Less than 80, greater than 30.	5
Moderate impairment	Less than or equal to 30, greater than 10.	2,5
Severe impairment Normally these patients will be on dialysis*	Less than or equal to 10.	2,5 mg on dialysis days**

* See section 4.4 – Haemodialysis patients.

** Enalaprilat is dialysable. Dosage on non-dialysis days should be adjusted depending on the blood pressure response.

Patients with renal insufficiency may require reduced and/or less frequent doses of NATRAPRESS (see section 4.4).

Heart failure/Asymptomatic left ventricular dysfunction

The initial dose of NATRAPRESS in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2,5 mg enalapril maleate, and it should be administered under close medical supervision to determine the initial effect on the blood pressure. In the absence of, or after effective management of, symptomatic hypotension following initiation of therapy with NATRAPRESS in heart failure, the dose of NATRAPRESS should be increased gradually

to the usual maintenance dose of 20 mg, given in a single dose or two divided doses, as tolerated by the patient.

The dose titration may be performed over a 2 to 4 week period, or more rapidly if indicated by the presence of residual signs and symptoms of heart failure. The patients with symptomatic heart failure, this dosage regimen was effective in reducing mortality.

Blood pressure, renal function should be monitored closely before and after treatment with NATRAPRESS (see section 4.4) because hypotension and consequent renal failure have been reported. In patients treated with diuretics the dosage should be reduced if possible before beginning treatment with NATRAPRESS. The appearance of hypotension after the initial dose of NATRAPRESS does not imply that hypotension will recur during chronic therapy with NATRAPRESS and does not preclude continued use of NATRAPRESS.

Serum potassium also should be monitored (see section 4.5).

4.3 Contraindications

- Hypersensitivity to enalapril or any of the ingredients of NATRAPRESS (see section 6.1).
- 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 below 30 ml/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section4.5).
- Porphyria.

- Lithium therapy: Concomitant administration with NATRAPRESS may lead to toxic blood concentration of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- The concomitant use of NATRAPRESS 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 NATRAPRESS, the treatment must be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Symptomatic hypotension

Symptomatic hypotension may occur especially in patients who are volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see sections 4.5 and 4.8).

In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of NATRAPRESS and/or diuretic is adjusted.

Similarly, patients with ischaemic heart or cerebrovascular disease may develop an excessive fall in blood pressure which could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in the supine position and, if necessary, an intravenous infusion of normal saline may be administered. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure is increased after volume expansion.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with NATRAPRESS. This effect is anticipated, and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of NATRAPRESS may be necessary (see section 4.2).

Aortic stenosis/ Hypertrophic cardiomyopathy

NATRAPRESS is contraindicated in patients with obstruction in the outflow tract of the left ventricle (See section 4.3).

Impaired renal function

Patients with renal insufficiency may require reduced and/or less frequent doses of NATRAPRESS**.** Careful dose titration and monitoring of renal function should be done (see section 4.2).

Some patients, with no apparent pre-existing renal disease have developed minor and usually transient increases in blood urea and serum creatinine when NATRAPRESS has been given concomitantly with a diuretic. Dosage reduction of NATRAPRESS and/or discontinuation of the diuretic may be required.

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients following treatment with NATRAPRESS. This may occur at any time during treatment. In such cases, NATRAPRESS should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airways obstruction, appropriate therapy which may include subcutaneous epinephrine solution 1:1 000 (0,3 to 0,5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be increased risk of angioedema while receiving ACE inhibitors including NATRAPRESS (see also section 4.3).

Black patients receiving NATRAPRESS have been reported to have a higher incidence of angioedema compared to non-black patients.

Patients receiving co-administration of NATRAPRESS and mTOR (mammalian target of rapamycin) inhibitor (e.g. temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema (see section 4.5).

Anaphylactoid reactions during hymenoptera desensitisation

Some patients receiving ACE inhibitors, including NATRAPRESS during desensitisation with hymenoptera venom have experience life threatening anaphylactoid reactions. Temporarily withholding ACE inhibitor therapy prior to each desensitisation, can help avert such reactions.

Anaphylactoid reactions during LDL Apheresis

Some patients receiving ACE inhibitors, including NATRAPRESS during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding NATRAPRESS therapy prior to each apheresis.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g. AN 69®) and treated concomitantly with NATRAPRESS. It is recommended that in these

patients a different type of dialysis membrane or a different class of antihypertensive medicine should be used.

Cough

Cough has been reported with the use of ACE inhibitors, including NATRAPRESS. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with medicines that produce hypotension, NATRAPRESS blocks angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Serum potassium

See section 4.5.

Hepatic failure

Patients receiving NATRAPRESS who develop jaundice or marked elevations of hepatic enzymes should discontinue the NATRAPRESS and receive appropriate medical follow-up.

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors, including NATRAPRESS. NATRAPRESS should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors,

especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy.

Hypoglycaemia

Diabetic patients treated with oral antidiabetic medicines or insulin starting NATRAPRESS, should be told to closely monitor for hypoglycaemia, especially during the first month of combined use (see section 4.5).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of NATRAPRESS and aliskiren is therefore contraindicated (see section 4.3).

Ethnic differences

NATRAPRESS is apparently less effective in lowering blood pressure in black patients than in non-black patients, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Information about excipients

NATRAPRESS contains lactose monohydrate (see section 6.1) which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take NATRAPRESS.

4.5 Interactions with other medicines and other forms of interactions

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 used 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).

Antihypertensive therapy

The combination of NATRAPRESS with other antihypertensive medicines may increase the antihypertensive effect, especially in combination with diuretics.

The combination of NATRAPRESS with beta-adrenergic blocking medicines and methyldopa or calcium entry blockers potentiates the hypotensive effects of NATRAPRESS.

Ganglionic blocking medicines or adrenergic blocking medicines, combined with NATRAPRESS, should only be administered with careful observation of the patient.

Because of lack of experience, concomitant treatment of NATRAPRESS with calcium antagonists is not recommended.

Concomitant use with nitroglycerine and other nitrates, or other vasodilators may increase the risk of hypotension.

Serum potassium

Risk factors for the development of hyperkaleamia include renal insufficiency, diabetes mellitus and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements, or potassium containing salt substitutes (see section 4.3).

In patients with renal failure, the administration of NATRAPRESS may lead to elevation of serum potassium. The use of potassium supplements, potassium sparing diuretics or potasssium containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium (see section4.3). If concomitant use of the above mentioned medicines is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Lithium

Lithium elimination may be reduced (see section 4.3).

Non-Steroidal Anti-Inflammatory Drugs

Patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of NATRAPRESS may result in a further deterioration of renal function. These effects are usually reversible.

Tricyclic antidepressants, antipsychotics, anaesthetics, narcotics

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with NATRAPRESS may result in further reduction of blood pressure (see section 4.4).

Gold

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

Mammalian Target of Rapamycin CmTORI Inhibitors

Patients taking concomitant mTOR inhibitor (e.g. temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema (see section 4.4).

Sympathomimetics

Since sympathomimetics may reduce the antihypertensive effects of NATRAPRESS, careful monitoring of blood pressure should occur when these medicines are used concomitantly with NATRAPRESS.

Antidiabetics

Concomitant administration of NATRAPRESS and antidiabetic medicines (insulins, oral hypoglycaemic medicines) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment (see section 4.4).

Alcohol

Alcohol enhances the hypotensive effect of concomitantly administered NATRAPRESS.

4.6 Fertility, pregnancy and lactation

See sections 4.3 and 4.4.

The use of NATRAPRESS is contraindicated during pregnancy. Pregnant woman should be informed of the potential hazards to the foetus and must not take NATRAPRESS during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with NATRAPRESS should be stopped immediately and if appropriate, alternative therapy should be started.

Foetal exposure to ACE inhibitors 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.

NATRAPRESS passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, hyperkalaemia, oliguria and anuria in newborns, have been reported after administration of NATRAPRESS in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

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

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur (see section 4.8).

4.8 Undesirable effects

Blood and lymphatic system disorders

Less frequent: Decreased haemoglobin, decreased haematocrit, decreased white blood cell count, bone marrow suppression, anaemia, thrombocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia, lymphadenopathy, autoimmune diseases.

Endocrine disorders

Frequency not known: Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Metabolism and nutrition disorders

Frequent: Hyperkalaemia.

Less frequent: Hyponatraemia, hypoglycaemia.

Nervous system disorders

Frequent: Headache, syncope.

Less frequent: Vertigo, paraesthesia, somnolence.

Psychiatric disorders:

Frequent: Mood alterations, depression.

Less frequent: Mental confusion, sleep disturbances, nervousness, dream abnormality, insomnia.

Eye disorders

Frequent: Blurred vision.

Ear and labyrinth disorders

Less frequent: Tinnitus

Cardiac disorders

Frequent: Myocardial infarction, tachycardia, chest pain, angina pectoris.

Less frequent: Palpitations, cerebrovascular accident

Vascular disorders

Frequent: Dizziness, orthostatic effects (including excessive hypotension).

Less frequent: Flushing, Raynaud's syndrome.

Respiratory, thoracic and mediastinal disorders

Frequent: Cough, dyspnoea.

Less frequent: Rhinitis, rhinorrhoea, sinusitis, sore throat, hoarseness, bronchospasm/asthma, pulmonary infiltrates, pneumonia, allergic alveolitis.

Gastrointestinal disorders

Frequent: Nausea, diarrhoea, abdominal pain, taste disturbances.

Less frequent: Ileus, pancreatitis, vomiting, indigestion, dry mouth, constipation, anorexia, stomatitis, glossitis, intestinal angioedema, gastric irritations, peptic ulcer.

Hepatobiliary disorders

Less frequent: Hepatitis (hepatocellular or cholestatic) jaundice, hepatic failure.

Skin and subcutaneous tissue disorders

Frequent: Rash, angioedema, which may be fatal, of the face, extremities, lips, tongue, glottis and/or larynx (see section 4.4).

Less frequent: Diaphoresis, alopecia, pruritus, urticaria, psoriasis, erythema multiforme, severe skin disorders including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and exfoliative dermatitis.

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA (Anti-Nuclear Antibody), elevated ESR (Erythrocyte Sedimentation Rate), eosinophilia, and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

Musculoskeletal and connective tissue disorders

Less frequent: Muscle cramps.

Renal and urinary disorders

Less frequent: Renal dysfunction, renal failure, oliguria, uraemia, anuria.

Reproductive system and breast disorders

Less frequent: Impotence, gynaecomastia.

General disorders and administration site conditions

Frequent: Asthenia, fatigue, malaise, fever.

Investigations

Frequent: Increases in serum creatinine, hyperkalaemia.

Less frequent: Increases in blood urea, increases in liver enzymes and/or bilirubin.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. 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 of overdose

Hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdosage of NATRAPRESS may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

Treatment of overdose

Treatment is symptomatic and supportive. Recommended treatment of overdosage is intravenous infusion of normal saline solution. If available, angiotensin II infusion may be beneficial. If ingestion is recent, induce emesis.

Enalaprilat may be removed from the general circulation by haemodialysis (see section 4.4, "Haemodialysis patients").

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 7.1.3 Vascular medicines - other hypotensives

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC Code: C09A A02

5.1 Pharmacodynamic properties

Enalapril maleate is a derivative of two amino acids, L-alanine and L-proline. Following oral absorption enalapril maleate is hydrolysed to enalaprilat, which is a specific, long-acting, non-sulphydryl angiotensin converting enzyme inhibitor.

Enalapril maleate 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.

ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

5.2 Pharmacokinetic properties

Absorption

Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril is approximately 60 %.

The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours. The absorption of oral enalapril is not influenced by the presence of food in the gastrointestinal tract. The extent of absorption and hydrolysis of enalapril are similar for the various doses in the recommended therapeutic range. In subjects with normal renal function, steady state serum concentrations of enalaprilat were achieved by the fourth day of administration of oral enalapril.

Biotransformation

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Similar peak serum concentrations of enalaprilat occur about 4 hours after an oral dose of enalapril.

Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril.

Elimination

Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40 % of the dose, and intact enalapril.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn starch, lactose monohydrate, maleic acid, hydroxypropyl methyl cellulose and zinc stearate.

NATRAPRESS 10 contains the colourant ferric oxide red and NATRAPRESS 20 contains ferric oxide red and ferric oxide yellow.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store at or below 25 °C in the original package. Protect from light.

Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

The film-coated tablets are packed in Aluminium/Aluminium foil blister strips. The blister strips are packed in cartons containing 28 or 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Smart Pharmaceuticals (Pty) Ltd

247 Voortrekker Road

Kraaifontein, Cape Town

7570

8. REGISTRATION NUMBERS

NATRAPRESS 5 mg: 46/7.1.3/1001

NATRAPRESS 10 mg: 46/7.1.3/1002

NATRAPRESS 20 mg: 46/7.1.3/1003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 September 2022

NAT/C/PI/A