PHYSICIANS CIRCULAR

Tablets

NOVATEC™
(lisinopril, USP)

NOVATEC (lisinopril, USP), a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme (ACE) inhibitor. NOVATEC inhibits ACE, resulting in decreased plasma angiotensin II and decreased aldosterone excretion, the consequence of which is a reduction of blood pressure in hypertensive patients and improvement in the signs and symptoms of congestive heart failure.

NOVATEC does not bind to plasma proteins other than ACE, is not metabolized in the body, and is excreted unchanged entirely in the urine.

INDICATIONS

- NOVATEC is indicated in the treatment of essential hypertension and in renovascular hypertension. It may be used alone or concomitantly with other classes of antihypertensive agents.

- NOVATEC is indicated in the management of heart failure as adjunctive treatment with diuretics and, where appropriate, digitalis.

- NOVATEC is indicated for the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction, to prevent the subsequent development of left ventricular dysfunction or heart failure and to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blocker.

DOSAGE AND ADMINISTRATION

Since absorption of Tablets NOVATEC is not affected by food, the tablets may be administered before, during or after meals. NOVATEC should be administered in a single daily dose. As with all single daily dose medications, NOVATEC should be taken at approximately the same time each day.

ESSENTIAL HYPERTENSION

In patients with essential hypertension the usual recommended starting dose is 10 mg. The usual effective maintenance dosage is 20 mg administered in a single daily dose. Dosage should be adjusted according to blood pressure response. In some patients, achievement of optimal blood pressure reduction may require two to four weeks of therapy. The maximum dose used in long term, controlled clinical trials was 80 mg/day.

A lower starting dose is required in the presence of renal impairment; in patients in whom diuretic therapy cannot be discontinued; patients who are volume and/or salt-depleted for any reason; and in patients with renovascular hypertension.

DIURETIC-TREATED PATIENTS

Symptomatic hypotension may occur following initiation of therapy with NOVATEC; this is more likely in patients who are being treated currently with diuretics. Caution is recommended, therefore, since these patients may be volume- and/or salt-depleted. The diuretic should be discontinued 2 to 3 days before beginning therapy with NOVATEC (see PRECAUTIONS). In hypertensive patients in whom the diuretic cannot be discontinued, therapy with NOVATEC should be initiated with a 5 mg dose. The subsequent dosage of NOVATEC should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

DOSAGE ADJUSTMENT IN RENAL IMPAIRMENT

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in Table 1.

Table 1

Creatinine Clearance (mL/min)	**Starting Dose (mg/day)**
≤ 70 > 30 mL/min	5 -10 mg
≤ 30 ≥ 10 mL/min	2.5 - 5 mg
< 10 mL/min (including patients on dialysis)**	2.5 mg*

* Dosage and/or frequency of administration should be adjusted depending on the blood pressure response.
**See PRECAUTIONS - Hemodialysis Patients

The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

RENOVASCULAR HYPERTENSION

Some patients with renovascular hypertension, especially those with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, may develop an exaggerated response to the first dose of NOVATEC. Therefore, a lower starting dose of 2.5 or 5 mg is recommended. Thereafter, the dosage may be adjusted according to the blood pressure response.

CONGESTIVE HEART FAILURE

The initial dose of NOVATEC in patients with heart failure is 2.5 mg given once a day. The usual effective dosage range is 5 to 20 mg per day administered in a single daily dose. In clinical trials, dosages were adjusted at 4-week intervals in patients requiring additional therapeutic effect. Dosage adjustments should be based on the clinical response of each individual patient. NOVATEC may be used in the management of heart failure as adjunctive treatment with diuretics and, where appropriate, digitalis.

Patients at high risk of symptomatic hypotension, e.g. patients with salt depletion with or without hyponatremia, patients with hypovolemia or patients who have been receiving vigorous diuretic therapy,

should have these conditions corrected, if possible, prior to therapy with NOVATEC. The effect of the starting dosage of NOVATEC on blood pressure should be monitored carefully.

ACUTE MYOCARDIAL INFARCTION

Treatment with NOVATEC may be started within 24 hours of the onset of symptoms. The first dose of NOVATEC is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily thereafter. Patients with a low systolic blood pressure (120 mmHg or less) when treatment is started or during the first 3 days after the infarct should be given a lower dose - 2.5 mg orally (see PRECAUTIONS). If hypotension occurs (systolic blood pressure less than or equal to 100 mmHg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mmHg for more than 1 hour) NOVATEC should be withdrawn. Dosing for patients with acute myocardial infarction should continue for six weeks. For patients who develop symptoms of heart failure, see DOSAGE AND ADMINISTRATION, CONGESTIVE HEART FAILURE.

NOVATEC is compatible with intravenous or transdermal glyceryl trinitrate.

PEDIATRIC PATIENTS

For patients who can swallow tablets, the dose should be individualized according to patient profile and blood pressure response. The recommended initial dose is 2.5 mg in patients 20 to <50 kg and 5 mg in patients ≥50 kg. PRINIVIL is given once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 20 mg daily in patients 20 to <50 kg and 40 mg in patients ≥50 kg.

CONTRAINDICATIONS

NOVATEC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioneurotic edema relating to previous treatment with an angiotensin-converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

PRECAUTIONS

SYMPTOMATIC HYPOTENSION

Symptomatic hypotension was seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving NOVATEC, hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting (see DRUG INTERACTIONS and SIDE EFFECTS). In patients with congestive 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, hyponatremia 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 NOVATEC and/or diuretic is adjusted. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to

further doses, which can be given usually without difficulty once the blood pressure has 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 NOVATEC. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of NOVATEC may be necessary.

HYPOTENSION IN ACUTE MYOCARDIAL INFARCTION

Treatment with lisinopril must not be initiated in acute myocardial infarction patients who are at risk of further serious hemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mmHg or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mmHg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic blood pressure is 100 mmHg or lower. If hypotension persists (systolic blood pressure less than 90 mmHg for more than 1 hour) then NOVATEC should be withdrawn.

AORTIC STENOSIS/HYPERTROPHIC CARDIOMYOPATHY

As with all vasodilators, ACE inhibitors should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

RENAL FUNCTION IMPAIRMENT

In patients with congestive heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases of blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when NOVATEC has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or NOVATEC may be required.

In acute myocardial infarction, treatment with lisinopril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with NOVATEC (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of NOVATEC.

HYPERSENSITIVITY/ANGIONEUROTIC EDEMA

Angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including NOVATEC. This may occur at any time during treatment. In such cases, NOVATEC should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient.

Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures to ensure a patent airway should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-Blacks.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (Also see CONTRAINDICATIONS).

ANAPHYLACTOID REACTIONS DURING HYMENOPTERA DESENSITIZATION

Rarely, patients receiving ACE inhibitors during desensitization with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitization.

HEMODIALYSIS PATIENTS

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

COUGH

Cough has been reported with the use of ACE inhibitors. 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/ANESTHESIA

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, NOVATEC may block 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.

HYPERKALEMIA - See also DRUG INTERACTIONS, SERUM POTASSIUM

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

The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal, arrhythmias.

If concomitant use of NOVATEC and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

HYPOGLYCEMIA

Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycemia, especially during the first month of combined use. (See DRUG INTERACTIONS.)

USE IN THE ELDERLY

In clinical studies, there was no age-related change in the efficacy or safety profile of the drug. When advanced age is associated with decrease in renal function, however, the guidelines set out in Table 1 (see DOSAGE AND ADMINISTRATION, Dosage Adjustment in Renal Impairment) should be used to determine the starting dose of NOVATEC. Thereafter, the dosage should be adjusted according to the blood pressure response.

USE IN PREGNANCY

The use of NOVATEC during pregnancy is not recommended. When pregnancy is detected, NOVATEC should be discontinued as soon as possible, unless it is considered life-saving for the mother.

In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor drug during the first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated.

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters. Use of ACE inhibitors during this period has been associated with fetal and neonatal injury including hypotension, renal failure, hyperkalemia, and/or skull hypoplasia in the newborn. Maternal oligohydramnios, presumably representing decreased fetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development. If NOVATEC is used, the patient should be apprised of the potential hazard to the fetus.

These adverse effects to the embryo and fetus do not appear to have resulted from intrauterine ACE-inhibitor exposure limited to the first trimester.

In those rare cases where ACE inhibitor use during pregnancy is deemed essential, serial ultrasound examinations should be performed to assess the intraamniotic environment. If oligohydramnios is detected, NOVATEC should be discontinued unless it is considered life-saving for the mother. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants whose mothers have taken NOVATEC should be closely observed for hypotension, oliguria and hyperkalemia. Lisinopril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

NURSING MOTHERS

It is not known whether NOVATEC is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised if NOVATEC is given to a nursing mother.

PEDIATRIC USE

Safety and effectiveness of NOVATEC in children have not been established.

Antihypertensive effects of PRINIVIL have been established in hypertensive pediatric patients aged 2 months to 16 years. Use of PRINIVIL in these age groups is supported by evidence from adequate and well-controlled studies of PRINIVIL in pediatric and adult patients as well as by literature in pediatric patients.

A multiple-dose pharmacokinetic study was conducted in 46 hypertensive male and female pediatric patients (infants through adolescents aged 6 months to <16 years) following daily oral administration of approximately 0.1 to 0.2 mg/kg lisinopril. At steady state, the mean urinary recovery of total lisinopril in 24 hours was 27.6% of the administered dose. The overall results of this study indicate that the pharmacokinetics of lisinopril in hypertensive children aged 6 months to <16 years are generally similar across the studied age groups and generally comparable to pharmacokinetic historic data in healthy adults.

In a clinical study involving 115 hypertensive pediatric patients 5 to 16 years of age, patients who weighed <50 kg received either 0.625, 2.5 or 20 mg of lisinopril daily and patients who weighed ≥50 kg received either 1.25, 5 or 40 mg of lisinopril daily. Lisinopril administered once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive effect of lisinopril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied, 0.625 mg (in patients <50 kg) and 1.25 mg (in patients ≥50 kg), corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients. In this study, lisinopril was generally well tolerated.

PRINIVIL is not recommended in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m^2 or in neonates as no data are available.

DRUG INTERACTIONS

DIURETICS

When a diuretic is added to the therapy of a patient receiving NOVATEC, the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure when NOVATEC is added. The possibility of symptomatic hypotension with NOVATEC can be minimized by discontinuing the diuretic prior to initiation of treatment with NOVATEC (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

OTHER AGENTS

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function. These effects are usually reversible.

NOVATEC has been used concomitantly with nitrates without evidence of clinically significant adverse interactions.

As with other drugs which eliminate sodium, lithium elimination may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered.

SERUM POTASSIUM – See also PRECAUTIONS, HYPERKALEMIA

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalemia did occur in some cases.

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

The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium.

If concomitant use of NOVATEC and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

If NOVATEC is given with a potassium-losing diuretic, diuretic-induced hypokalemia may be ameliorated.

ANTIDIABETICS
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment. In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored for hypoglycemia, especially during the first month of treatment with an ACE inhibitor.

GOLD

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

SIDE EFFECTS

NOVATEC has been found in controlled clinical trials to be generally well tolerated. For the most part, side effects were mild and transient in nature.

The most frequent clinical side effects of NOVATEC in controlled trials were: dizziness, headache, diarrhea, fatigue, cough, and nausea. Other side effects occurring less frequently were: orthostatic effects (including hypotension), rash, and asthenia.

Hypersensitivity/Angioneurotic Edema
Angioneurotic edema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported rarely (see PRECAUTIONS). In very rare cases, intestinal angioedema has been reported with angiotensin converting enzyme inhibitors including lisinopril.

Side effects which occurred rarely, either during controlled clinical trials or after the drug was marketed, include:

CARDIOVASCULAR
myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients (see PRECAUTIONS)
palpitation
tachycardia

DIGESTIVE
abdominal pain
dry mouth
pancreatitis
hepatitis - either hepatocellular or cholestatic
jaundice

ENDOCRINE
syndrome of inappropriate antidiuretic hormone secretion (SIADH)

METABOLIC
Cases of hypoglycemia in diabetic patients on oral antidiabetic agents or insulin have been reported (see DRUG INTERACTIONS)

NERVOUS SYSTEM
mood alterations
mental confusion
paresthesia

RESPIRATORY
bronchospasm

SKIN
urticaria
pruritus
diaphoresis
alopecia

UROGENITAL
uremia
oliguria/anuria
renal dysfunction
acute renal failure

impotence

A symptom complex has been reported which may include some or all of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity, or other dermatologic manifestations may occur.

PEDIATRIC PATIENTS

The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients.

LABORATORY TEST FINDINGS

Clinically important changes in standard laboratory parameters were rarely associated with administration of NOVATEC. Increases in blood urea, serum creatinine, liver enzymes and serum bilirubin usually reversible upon discontinuation of NOVATEC, have been seen.

Bone marrow depression, manifest as anemia and/or thrombocytopenia and/or leukopenia, has been reported.

Small decreases in hemoglobin and hematocrit, rarely of clinical importance unless another cause of anemia coexisted, have occurred.

Hyperkalemia and hyponatremia have occurred.

OVERDOSAGE

The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution, if available, angiotensin II may be beneficial. Lisinopril may be removed from the general circulation by hemodialysis. (See PRECAUTIONS, Hemodialysis Patients.)

AVAILABILITY

NOVATEC Tablets 5 mg and 10 mg are supplied in blister packs of 30’s each (10’s x 3 strips)