

## **PREFACE TABLETS [2.5 & 5mg]**

### **COMPOSITION:**

Each uncoated tablet contains Ramipril USP equivalent to Ramipril (anhydrous) 2.5/5 mg

### **DESCRIPTION:**

Ramipril is a long acting specific inhibitor of angiotensin converting enzyme, which catalyses the conversion of the inactive decapeptide angiotensin I to the active angiotensin II. Inhibition of ACE results in decreased angiotensin II which leads to decreased vasopressor activity and aldosterone secretion. Thus, Ramipril reduces both cardiac output and peripheral resistance, and thus reduces blood pressure. The effect of ramipril on hypertension appears to result at least in part from inhibition of both tissue and circulating ACE activity, thereby reducing angiotensin II formation in tissue and plasma.

### **PHARMACOKINETICS:**

**Ramipril is almost completely metabolized to Ramiprilat**, which has about 6 times the ACE inhibitory activity of ramipril, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive. After oral administration of ramipril, about 60% of the parent drug and its metabolites are eliminated in the urine, and about 40% is found in the feces. Drug recovered in the feces may represent both biliary excretion of metabolites and/or unabsorbed drug, however the proportion of a dose eliminated by the bile has not been determined. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

<b>Parameter</b>	<b>Value</b>
<b>T<sub>max</sub></b>	Within one hour
<b>Onset of action</b>	Within 1-2 hours
<b>Time for Peak effect</b>	4-6.5 hours
<b>T<sub>1/2</sub></b>	5.1 hours
<b>Duration of action</b>	24 hours
<b>Absorption</b>	50-60%
<b>Bioavailability</b>	Ramipril 28% & Ramiprilat 44%
<b>Protein binding</b>	73% for Ramipril & 56% for Ramiprilat

After once-daily dosing, steady-state plasma concentrations of ramiprilat are reached by the fourth dose. Steady-state concentrations of ramiprilat are somewhat higher than those seen after the first dose of **PREFACE**, especially at low doses (2.5 mg), but the difference is clinically insignificant.

### **PHARMACODYNAMICS**

Single doses of **PREFACE** of 2.5–20 mg produce approximately 60–80% inhibition of ACE activity 4 hours after dosing with approximately 40–60% inhibition after 24 hours. Multiple oral doses of ramipril of 2.0 mg or more cause plasma ACE activity to fall by more than 90% 4 hours after dosing, with over 80% inhibition of ACE activity remaining 24 hours after dosing. The more prolonged effect of even small

multiple doses presumably reflects saturation of ACE binding sites by ramiprilat and relatively slow release from those sites.

#### **INDICATIONS:**

- \* **PREFACE** is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.
- \* **PREFACE** is indicated in stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining acute myocardial infarction. Administration of ramipril to such patients has been shown to decrease the risk of death (principally cardiovascular death) and to decrease the risks of failure-related hospitalization and progression to severe/resistant heart failure.
- \* **PREFACE** is indicated in patients 55 years or older at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria), to reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes.

#### **DOSAGE AND ADMINISTRATION:**

**Hypertension:** The recommended initial dosage is 2.5mg of **PREFACE** daily. Dosage should be adjusted according to the blood pressure response. The usual maintenance dosage range is 2.5 to 20mg per day administered as a single dose or in two equally divided doses.

**Heart Failure Post Myocardial Infarction:** For the treatment of post-infarction patients who have shown signs of congestive failure, the recommended starting dose of **PREFACE** is 2.5mg twice daily (5mg per day).

**Standard Risk Reduction programme:** **PREFACE** should be given at an initial dose of 2.5 mg, once a day for 1 week, 5 mg, once a day for the next 3 weeks, and then increased as tolerated, to a maintenance dose of 10 mg, once a day. If the patient is hypertensive or recently post myocardial infarction, it can also be given as a divided dose.

**Dosage Adjustment in Renal Impairment:** In patients with GFR <40 ml/min/1.73m<sup>2</sup> (serum creatinine approximately >2.5 mg/dl) doses only 25% of those normal dose of **PREFACE** should be used should be expected to induce full therapeutic levels of ramiprilat.

#### **CONTRAINDICATIONS:**

**PREFACE** is contraindicated in patients who are hypersensitive to this product or any other angiotensin converting enzyme inhibitor.

## **DRUG INTERACTIONS:**

**Diuretics:** Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with

## **PREFACE.**

**Agents increasing serum potassium:** Ramipril attenuates potassium loss. Use of **PREFACE** with potassium sparing diuretics, potassium supplements, or potassium containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

**Lithium:** Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs, which cause elimination of sodium. Ramipril increases sodium excretion.

**NSAID:** Rarely, concomitant treatments with ACE inhibitors and nonsteroidal anti-inflammatory agents have been associated with worsening of renal failure and an increase in serum potassium.

## **PRECAUTIONS:**

### **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats for up to 24 months at doses of up to 500 mg/kg/day or to mice for up to 18 months at doses of up to 1000 mg/kg/day.

### **Pregnancy**

Pregnancy Categories C (first trimester) and D (second and third trimesters).

### **Lactation**

Ingestion of single 10 mg oral dose of **PREFACE** resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, women receiving **PREFACE** should not breast feed.

### **Geriatrics**

No safety differences were observed in comparison to general population.

### **Pediatrics**

Safety and effectiveness in pediatric patients have not been established. Irreversible kidney damage has been observed in very young rats given a single dose of ramipril.

### **Renal impairment:**

**PREFACE** should be used with caution in patients with severe renal disease. As a consequence of inhibition of the renin-angiotensin-aldosterone system (RAAS), changes in renal function may be anticipated in susceptible individuals. In hypertensive patients with unilateral or bilateral renal stenosis, increases in blood urea nitrogen and serum creatinine may occur which is usually reversible. When such

patients are treated with the combination, renal function should be monitored during the first few weeks of therapy.

**ADVERSE REACTIONS:**

**Cardiovascular:** Symptomatic hypotension [in 0.5% of cases]

**Hematologic:** Pancytopenia, hemolytic anemia and thrombocytopenia.

**Renal:** Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking **PREFACE**, particularly when **PREACE** was given concomitantly with a diuretic.

**Angioedema:** is noted in 0.3% cases In such cases, **PREFACE** should be promptly discontinued.

**Gastrointestinal:** Hepatic failure, hepatitis, jaundice, pancreatitis, abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, increased salivation and taste disturbance.

**Overdosage**

Therapy with the combination should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

**Presentation**

**PREFACE** is available in two strengths of 2.5 & 5 mg in a blister pack of 10 tablets