# PENDORIL®

Perindopril Erbumine

**NAME OF THE MEDICINAL PRODUCTS**

**PENDORIL®** tablets are available in 2mg and 4mg strength for oral administration.

**COMPOSITION**

Perindopril 2mg and 4mg as Perindopril Erbumine.

**DESCRIPTION**

**PENDORIL®** (Perindopril Erbumine) is the tert-butylamine salt of perindopril, the ethyl ester of a nin-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor.

**CLINICAL PHARMACOLOGY**

*Mechanism of Action:* **PENDORIL®** (Perindopril Erbumine) tablet is a prodrug for perindoprlat, which inhibits ACE in human subjects and animals. The through which perindoprlat lowers blood pressure is believed to be primarily inhibition of ACE activity. The principal mechanism of perindopril in blood pressure reduction is believed to be through the rennin-angiotensin-aldosterone system. After administration of perindopril, ACE is inhibited in a dose and blood-concentration fashion, with the maximal inhibition of 80 to 90% attained by 8mg persisting for 10 to 12 hours. It also inhibits Tissue Converting Enzyme. Thus it improves the ratio of elasitin to collagen and remodels artrioles.

**PHARMACOKINETICS**

Oral administration of **PENDORIL®** (Perindopril Erbumine) tablets results in its rapid absorption occurring at approximately 1 hour. The absolute oral bioavailability of perindopril is about 75% following absorption, approximately 30 to 50% of systematically available perindopril is hydrolyzed to its active metabolite, perindoprilat, peak plasma concentrations of perindopril are attained 3 to 7 hours after perindopril administration. The presence of food in the gastrointestinal tract does not affect the rate or extent of absorption of perindopril but reduces bioavailability of perindopril by about 35%. The mean half-life of perindopril associated with most of its elimination is approximately 0.8 to 1 hours. Perindopril is extensively metabolized following oral administration, with only 4 to 12% of the dose recovered unchanged in the urine.

**PHARMACODYNAMICS**

In placebo-controlled studies of perindopril monotherapy in patient with a mean blood pressure of about 150/100 mm Hg, 2mg had little effect, but doses of 4 to 16 mg lowered blood pressure.

**INDICATION AND USAGE**

**PENDORIL®** (Perindopril Erbumine) tablets is indicated for the treatment of patients with essential hypertension. PENDORIL® tablets may be used alone or congestive heart failure (adjunctive therapy).

**CONTRAINDICATIONS**

**PENDORIL®** (Perindopril Erbumine) tablets is contraindicated for the treatment in patients known to be hypersensitive to this products or to any other ACE inhibitor. **PENDORIL®** tablet is also contraindicated in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

**WARNINGS**

Anaphylactoid and possibly related reaction: Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors may be subjected to a variety of adverse reaction.

*Angioedema:* Angioedema involving the face, extremities, lips, tongue, goiter and/or larynx has been reported in patientstreated with ACE inhibitors including Perindopril tablets. In such cases Perindopril tablets should be promptly discontinued and the patients carefylly observed until the swelling disappears.

Hypotension: Like other ACE inhibitors Perindopril tablets can cause symptomatic hypotension. Perindopril tablets has been associated with hypotension in 0.3% of uncomplicated hypertensive patients.

*Dry cough:* May occur and it is advised to consult a physician to decide if it is reasonable to continue the treatment.

**PRECAUTIONS**

*Impaired renal function:* As a consequence of inhibiting the rennin-angiotensin-aldosterone system , changes in renal function may be anticipated in susceptible individuals.

Hypertensive patients with congestive heart failure: In patients with severe congestive heart failure, where renal function may depend on the activity of the rennin-angiotensin-aldosterone system, treatment with ACE inhibitors including Perindopril tablets may be associated with Liguria and/or progressive azotemia, and rarely with acute renal failure and/or death.

Hypertensive patients with Renal Artery Stenosis: In hypertensive patients with unilateral or bilateral renal artery stenosis, increase in blood urea nitrogen and serum creatinine may occur, experience with ACE inhibitors suggests that these increases are usually reversible upon discontinuation of the drug. In such patients, renal function should be monitored during the first few weeks of therapy.

*Pregnancy:* Female patients of child bearing age should be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

**Nursing mother:** It is not known whether perindopril is secreted in human milk. Because many drugs are secreted in human milk, cautions should be exercised when Perindopril tablet is given to nursing mothers.

*Pediatric use:* Safety and effectiveness of Perindopril tablets in pediatric patients have not been established.

**DRUG INTERACTION:** *DIURETICS:* Patients on diuretics, and specially those started recently, may occasionally experience an excessive reduction of blood pressure after inhibition of Perindopril tablet therapy. The possibility of hypotensive effects can be minimized by either discontinuing the diuretic or increasing the salt intake prior to ignition of treatment with perindopril. If diuretics can not be interrupted, close medical supervision should be provided with the first dose of Perindopril® tablets for at least two hours and blood pressure has stabilized for another hour.

Carcinogenesis, Mutagenesis, Impairment of fertility:

*Carcinogenesis:* No evidence of carcinogenic effect was observed in studies in rats and mice when perindopril was administered at dosages up to 20 times (mg/kg) or 2 to 4 times (mg/m2) the maximum proposed clinical doses (16mg/days) for 104 weeks.

*Mutagenesis:* No genotoxic potential was detected for Perindopril tablets, perindopril and other metabolites in various in vitro and in vivo investigations, including the Ames test, the saccharomyces cerevisiae D4 test, cultured human lymphocytes, TK ± mouse lymphoma assay, mouse and micronucleus tests and Chinese hamster bone marrow assay.

*Geriatric use:* The mean blood pressure effect of perindopril was somewhat smaller in patients over 60 than in younger patients, although the difference was not significant. Plasma concentration of both perindopril and perindoprilat were increased in elderly patients compared to concentrations in younger patients. No adverse effect were clearly increased in older patients with the exception of dizziness and possibly rash. Experience with **PENDORIL®** tablets in elderly patients at daily doses exceeding 8mg is limited.

**ADVERSE REACTION**

Perindopril tablet is in general well tolerated, the side effects were usually mild and transient. Although dizziness was reported more frequently in placebo patients (8.5%) than in perindopril patients (8.2%), the incidence appeared to increase with an increase in perindopril dose. Adverse events that occurred in 1% or greater of the patients and that were more common for perindopril than placebo by at least 1%

**DOSAGE AND ADMINISTRATION**

*Use in systemic hypertensive patients:* In patients with essential hypertension, the recommended initial dose is 4mg once daily. The dosage may be litrated upward until blood pressure when measured just before the next dose, is controlled or to a maximum of 16mg/day. The usual maintenance dose range is 4 to 8 mg administered as a single daily dose.

*Congestive heart failure:* **PENDORIL®** should be started under close medical supervision at a starting dose of 2mg in the morning. This may be increased to 4mg once blood pressure acceptability has been demonstrated. Elderly patients start treatment at 2mg daily.

*Use in concomitant diuretics:* If blood pressure is not adequately controlled by perindopril alone, a diuretic may be added. In patients currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of perindopril.

*Use in patients with impaired renal function:* Kinetic data indicate that perindoprilat elimination is decreased in renally impaired patients, with a marked increase in accumulation when creatinine clearance drops below 30ml/min. For patients with lesser degrees of impairment (creatinine clearance should be above 30ml/min) the initial dosage should be 2 mg/day and dosage should not exceed 8 mg/day due to limited clinical experience.

**OVERDOSAGE**

In animals doses of perindopril up to 2500 mg/kg in mice, 3000 mg/kg in rats and 1600mg/kg in dogs were non-lethal. Past experiences were scant but suggested that over dosage with other ACE inhibitors was also fairly well tolerated by humans. The most likely manifestation is hypotension, and treatment should be discontinued and the patient should be served, dehydration, electrolyte imbalance and hypotension should be treated by established procedures.

***Shelf Life:*** 2 years from the date of manufacture.

*Pharmaceutical Precaution:* Store in a cool and dry place, away from light. Keep all medicines out of reach of children.

**Package quantities**

PENDORIL® 2 : 2 x 10 tablets in Alu-Alu blister.
PENDORIL® 4 : 2 x 10 tablets in Alu-Alu blister.

® Trade Mark

Manufactured by :
RENATA LIMITED
Dhaka-Bangladesh
Updated : April, 2012
C-Code No. : 5329/V 01