BIOPHARMACEUTICS ASSIGNMENT

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RAMIPRIL

DRUG MONOGRAPH

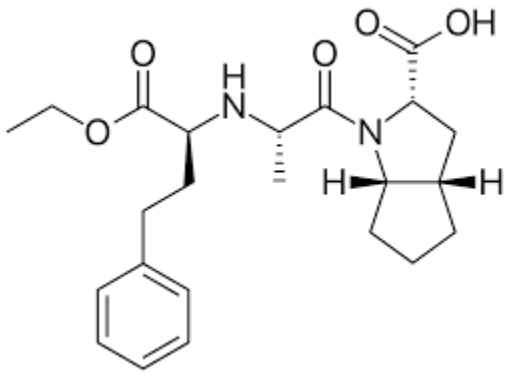
INTRODUCTION:

Ramipril is an ACE Inhibitor drug that is used for the management of hypertension and for the reduction of cardiovascular mortality that following the Myocardial Infarction in the hemodynamically stable patient with the clinical signs of congestive heart failure.

CHEMICAL FORMULA:

$C_{23}H_{32}N_2O_5$

STRUCTURAL FORMULA:



THERAPEUTIC CATEGORY:

- Angiotensin converting enzyme inhibitor
- Antihypertensive agents indicated for hypertension
- Agents action on Renin Angiotensin system

DOSAGE FORMS :

- It is available in the form of oral capsules and oral tablets.
- It is in the strength of 1.25mg , 2.5mg , 5mg and 10mg .

INDICATIONS:

- It is used for the treatment of hypertension.
- It helps to reduce cardiovascular mortality (risk of death from heart-related causes).
- It is prescribed after myocardial infarction (heart attack).
- It is specifically for hemodynamically stable patients.

- It is beneficial for those showing clinical signs of congestive heart failure.

MECHANISM OF ACTION :

Ramipril is a pro-drug that is converted in its active form **Ramiprilat** in the liver by the hepatic enzymes carboxylestrase.

ACE Inhibition: Ramiprilat inhibiting the angiotensin converting enzymes (ACE) which are responsible for the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor and and stimulating the secretion of aldosterone. By the inhibition of ACE, Ramiprilat decreases the formation of Angiotensin II, that are leading to vasodilation and decreases the secretion of aldosterone.

Bradykinin effect: Angiotensin-converting enzyme also degrades the bradykinin that is vasodilator. Inhibiting the ace increase the bradykinin levels that causes the side effects like persistent dry cough.

Hemodynamic Effects: The reduction in angiotensin II and increase in bradykinin result in vasodilation, decreased blood pressure, and reduced workload on the heart.

PHARAMCOKINETICS:

ABSORPTION:

The extent of absorption is at least about 50 to 60%. Food decreases the rate of absorption from the GI tract without affecting the extent of absorption.

The serum concentration of ramiprilat was unchanged when capsules were opened and the contents dissolved in water, dissolved in apple juice, or suspended in apple sauce.

BIOAVAILABILITY:

The absolute bioavailabilities of ramipril and ramiprilat were 28% and 44%, respectively, when oral administration was compared to intravenous administration.

VOLUME OF DISTRIBUTION:

Ramipril (prodrug) ~ 0.9 L/kg

Ramiprilat (active metabolite) ~ 0.8 L/kg

PROTEIN BINDING:

Protein binding of ramipril is about 73% and that of ramiprilat is about 56%.

METABOLISM:

The 25% of the hepatic metabolism produces the active metabolite ramiprilat via Liver Esterase enzyme.

EXCRETION:

About 60% of the drug is excreted in urine as unchanged form and 40% of the drug is found in feces that are representing both unabsorbed drug and the metabolites eliminated via biliary excretion in urine.

HALF LIFE:

The half life of ramiprilat is dose dependent after multiple daily doses (MDDs) , having a range of about **13-17 hours** with 5mg-10 mg MDDs to **27-36 hours** for 2.5 mg MDDs

CLEARANCE:

The mean renal clearance of ramipril and ramiprilat that is reported to be 10.7 and 126.8 Ml/min in healthy elderly patients with normal renal function.

ADVERSE EFFECT:

- Dry cough
- Neutropenia
- hyperkalemia
- Chest pain
- Mouth dryness
- Dizziness
- Lightheadedness
- Impotence
- Shakiness

CONTRAINDICATION:

It is contraindicated in the following conditions;

- Patient having Volume depletion
- History of angioedema with ACE inhibitors
- Hypotension
- Hyperkalemia

Pregnancy: Category D Interactions

Its use is not recommended during the 1st trimester and is contraindicated during the 2nd and 3rd trimesters.
This drug should not be used during pregnancy, because the use of this drug increased incidence of human fetal malformations or irreversible damage.

INTERACTIONS:

Interaction with food:

- Avoid potassium-containing products because Potassium products increase the risk of hyperkalemia.
- Take with or without food. Its absorption is unaffected by food.

Interactions with drug:

- Albuterol as the **salbutamol** may decreases the antihypertensive effects of ramipril.
- The risk or severity of renal failure, hyperkalemia, and hypertension can be increased when **Aceclofenac** is combined with Ramipril.

Interactions with disease:

- In **Renal artery stenosis** (bilateral or unilateral) it may be used but monitor renal function and serum creatinine closely.

OFF LABEL USE:

- Diabetic nephropathy
- Chronic kidney disease
- Prevention of migraine

DOSING SCHEDULE ACCORDING TO AGE AND DISEASES

Patient Group / Condition	Initial Dose	Maintenance Dose	Min Daily Dose	Max Daily Dose	Notes
Hypertension (Adults)	2.5 mg once daily (if not on diuretics) 1.25 mg once daily (if volume depleted)	2.5–20 mg/day (once or twice daily)	1.25 mg	20 mg	Titrate slowly. Monitor BP and renal function.
Heart Failure (Post-MI)	2.5 mg twice daily (or 1.25 mg if hypotensive)	Up to 5 mg twice daily	2.5 mg	10 mg	Begin within a few days post-MI.
CV Risk Reduction (Adults)	2.5 mg once daily (Week 1) 5 mg once daily (Weeks 2–4)	10 mg once daily	2.5 mg	10 mg	For patients at high cardiovascular risk.
Renal Impairment (CrCl < 40)	1.25 mg once daily	Titrate cautiously	1.25 mg	5 mg	Monitor creatinine and potassium.

Heart Failure + Renal Impairment	1.25 mg once daily	1.25–2.5 mg twice daily	1.25 mg	5 mg	Dose split recommended.
Elderly (65+)	Start with 1.25–2.5 mg daily	Adjust per response	1.25 mg	10–20 mg	Monitor closely due to higher risk of side effects.
Children (<18 years)	Not routinely recommended	—	—	—	Use only if directed by a pediatric specialist.
Patients on Diuretics	1.25 mg once daily	Adjust based on BP	1.25 mg	Based on condition	Withhold diuretic before initiating if possible.

COMMONLY AVAILABLE BRANDS IN PAKISTAN

Brands	Dosage form	Manufacturer
Ramipace	Tablet	Pharm Evo (PVT) LTD
Ramy	Tablet	Getz Pharma Pakistan
Tritace	Tablet	Sanofi Aventis LTD
Lipra	Tablet	Pfizer Laboratories

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