Imidapril hydrochloride

Vascor®

5 mg and 10 mg Tablet

℞

Angiotensin Converting Enzyme Inhibitor / Antihypertensive

FORMULATION

Each tablet contains:

Imidapril hydrochloride ……5 mg or 10 mg

PRODUCT DESCRIPTION

Vascor® 5 mg Tablet: White, round, biconvex tablet, 6 mm in diameter, bisected and debossed with "TA 135" on one side and debossed with "5" on the other side

Vascor® 10 mg Tablet: White, round, biconvex tablet, 6.5 mm in diameter, bisected and debossed with "TA 136" on one side and debossed with "10" on the other side

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Imidapril is an ester prodrug which is hydrolyzed after oral administration to form the active angiotensin-converting enzyme (ACE) inhibitor imidaprilat. Imidaprilat has potent ACE inhibitory effects, 1.2 times and 2.6 times that of enalaprilat and captopril, respectively.

Imidapril's blood pressure lowering effect is mainly due to ACE inhibition and consequent reduction in angiotensin II, resulting in dilatation of peripheral vessels and reduction in vascular resistance. The blood pressure lowering effect of imidapril is comparable to enalapril and five to ten times more potent than that of captopril.

Imidapril decreases total peripheral vascular resistance without an increase in heart rate or cardiac contractility. Imidapril increases renal blood flow and reduces renal vascular resistance mainly due to dilatation of the efferent arteriole. Imidapril showed no specific effect on the central nervous, digestive, respiratory, smooth muscle, reproductive, urologic, hematologic, and metabolic systems.

PHARMACOKINETICS

About 70% of imidapril is absorbed from the gastrointestinal tract and reaches peak plasma concentration within 2 hours after oral administration. Plasma imidapril concentrations decline monophasically with a half-life of about 2 hours. A fat-rich meal significantly decreases imidapril absorption.

Imidapril undergoes de-esterification in the liver to form imidaprilat. Peak plasma imidaprilat concentrations are reached within 7 hours, and decline biphasically with an initial half-life of 7 to 9 hours and a terminal half-life of more than 24 hours. The absolute bioavailability of imidaprilat is 42%. After multiple dosing, steady state imidaprilat concentrations are reached after 5 days. Protein binding of imidapril and imidaprilat is 85 and 53%, respectively.

After single oral dosing, imidapril absorption appeared linear with doses of 10 to 240 mg based on plasma and urinary excretion data. Drug elimination is primarily via renal (40%) and hepatobiliary (50%) routes.

Special Populations:

Renal Impairment

The experience in all grades of renal impairment is limited. Increased plasma levels and area under the curve (AUC) of imidapril and imidaprilat were reported in patients with renal impairment. There was a two-fold increase in the AUC of imidaprilat in patients with creatinine clearance 30 to 80 mL/min and an almost ten-fold increase in patients with creatinine clearance 10 to 29 mL/min.

Hepatic Impairment

In patients with hepatic impairment, the AUC of imidapril and imidaprilat were slightly higher than in normal subjects while the time to peak plasma concentration (Tmax) for both was similar in the two groups. The half-life of imidaprilat, but not that of imidapril, was significantly increased in patients with hepatic impairment.

INDICATIONS

- Essential (mild to moderate) and severe hypertension
- Congestive heart failure
- Proteinuria secondary to diabetic nephropathy

DOSAGE AND ADMINISTRATION

General Dosing Recommendations:

- Take orally at about the same time of day, 15 minutes before meals.
- Individualize dosage according to patient's clinical response.

INDICATIONS	RECOMMENDED ORAL IMIDAPRIL DOSE
Hypertension	**Adults** **Initial Dose:** 5 mg once daily • If blood pressure remains uncontrolled after 3 weeks of therapy, increase dose to 10 mg once daily (usual maintenance dose) • Maximum Dose: 20 mg once daily **Elderly (65 years or older)** **Initial Dose:** 2.5 mg once daily • Maximum Dose: 10 mg once daily **Patients with renal insufficiency (creatinine clearance between 30 mL/min and 80 mL/min) or hepatic impairment, and patients at increased risk for first dose hypotension:** **Initial Dose:** 2.5 mg once daily
Congestive Heart Failure	**Initial Dose:** 2.5 mg once daily • Maximum Dose: 10 mg once daily
Proteinuria/ Diabetic Nephropathy	**Initial Dose:** 2.5 mg once daily • Maximum Dose: 5 mg once daily
Or, as prescribed by a physician.	

CONTRAINDICATIONS

- Hypersensitivity to imidapril hydrochloride, any ACE inhibitor, or to any component of the product
- History of angioneurotic edema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Pregnancy
- Breastfeeding
- Renal failure with or without hemodialysis
- Concomitant use with aliskiren in patients with diabetes mellitus or renal impairment [glomerular filtration rate (GFR) <60 mL/min/1.73 m^2]

WARNINGS AND PRECAUTIONS

Fetal Toxicity: When pregnancy is detected, discontinue imidapril hydrochloride as soon as possible. Drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and death to the developing fetus.

Fetal Toxicity: The use of drugs that act on the renin-angiotensin-aldosterone system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue imidapril as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin-aldosterone system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin-aldosterone system for a particular patient, the mother should be informed of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue imidapril, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. However, physicians and patients should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to imidapril for hypotension, oliguria and hyperkalemia.

Infants with history of *in utero* exposure to an ACE inhibitor should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Hypotension: Imidapril, like other ACE inhibitors, may cause a profound fall in blood pressure particularly after the first dose. Symptomatic hypotension is observed rarely in patients with uncomplicated hypertension. In hypertensive patients treated with imidapril, 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). Symptomatic hypotension has also been observed in patients with heart failure (with or without associated renal insufficiency). This is most likely to occur in 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, treatment should be under medical supervision and patients should be monitored whenever the dose of imidapril and/or diuretic is adjusted. Apply similar considerations to patients with ischemic heart disease or cerebrovascular disease in whom an excessive fall in blood pressure may result in myocardial infarction or cerebrovascular accident.

If hypotension develops, place the patient in a supine position. Volume repletion with intravenous normal saline may be required. The appearance of hypotension after the initial dose does not preclude subsequent careful dose titration with imidapril after effective management.

Renovascular Hypertension: An increased risk of severe hypotension and renal impairment has been observed in patients with renovascular hypertension and pre-existing bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. Treatment of these patients should be under strict medical supervision, with low doses, careful titration, and monitoring of renal function.

Renal Impairment: Changes in renal function may be anticipated in susceptible individuals due to inhibition of the renin-angiotensin-aldosterone system. Thus, imidapril should be used with caution in patients with impaired renal function. Reduced doses are required for patients with creatinine clearance between 30 to 80 mL/min. Due to limited data, imidapril should not be given to patients with creatinine clearance <30 mL/min. Close monitoring of renal function during treatment should be performed.

Renal failure associated with ACE inhibitors has been reported mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. Some patients, with no apparent pre-existing renal disease, have developed minor and usually transient elevations in blood urea and serum creatinine when imidapril was coadministered with a diuretic. Reduction in imidapril dosage and/or discontinuation of the diuretic may be necessary. This situation should raise the possibility of underlying renal artery stenosis.

Kidney Transplantation: There is no data on the use of imidapril in patients with recent kidney transplantation.

Hemodialysis: Anaphylactoid reactions such as facial swelling, flushing, hypotension, and dyspnea have been seen in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Consider giving a different type of dialysis membrane or a different class of antihypertensive agent in these patients.

Hepatic Impairment: Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and sometimes death. The mechanism of this syndrome is not understood. Discontinue the ACE inhibitor and take appropriate medical measures if marked elevations of hepatic enzymes or jaundice occur.

Psoriasis: Imidapril, as with other ACE inhibitors, should be used with caution in patients with psoriasis.

Angioneurotic Edema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients receiving ACE inhibitors, including imidapril. Symptoms may occur at any time during treatment. In such cases, immediately discontinue imidapril and institute appropriate monitoring until complete and sustained resolution of symptoms has occurred.

Angioedema associated with laryngeal edema or tongue edema may be fatal. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, particularly those with a history of airway surgery. 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.

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

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors.

Anaphylactoid Reactions during Desensitization: There have been isolated reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (bees, wasps) venom. Discontinue imidapril before desensitization treatment.

Anaphylactoid Reactions during LDL-Apheresis: Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily discontinuing ACE inhibitor therapy prior to apheresis.

Aortic Stenosis/Hypertrophic Cardiomyopathy: Use with caution in patients with left ventricular valvular and outflow tract obstruction.

Neutropenia/Agranulocytosis: Neutropenia/agranulocytosis, thrombocytopenia and anemia have been observed rarely in patients receiving ACE inhibitors, including imidapril. Imidapril 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. If imidapril is used in such patients, white blood cell count and differential counts should be performed prior to therapy, every 2 weeks during the first 3 months of imidapril therapy, and periodically thereafter. Patients should be instructed to report any sign of infection (e.g., sore throat, fever) during treatment.

If neutropenia (neutrophils <1000/mm^3) is detected or suspected, imidapril and other concomitant medication should be discontinued. In most patients, neutrophil counts rapidly return to normal upon discontinuing imidapril therapy.

Cough: Persistent nonproductive cough has been reported with all ACE inhibitors, presumably due to the inhibition of the degradation of endogenous bradykinin. Cough always resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia: There are no data available on the use of imidapril under conditions of surgery or anesthesia. However, like other ACE inhibitors, imidapril may cause hypotension or even hypotensive shock in patients undergoing major surgery or during anesthesia. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalemia: Elevations in serum potassium have been observed in patients treated with ACE inhibitors, including imidapril. Risk factors for the development of hyperkalemia include:

- Renal insufficiency or worsening of renal function
- Age (> 70 years old)
- Diabetes mellitus
- Intercurrent events (i.e., dehydration, acute decompensation, metabolic acidosis)
- Concomitant use of potassium salts, potassium-sparing diuretics (e.g., amiloride, spironolactone, triamterene) or potassium supplements or those patients taking other drugs associated with increases in serum potassium (e.g., heparin)

Diabetic Complications: The blood glucose levels should be closely monitored for hypoglycemia in diabetic patients previously treated with oral antidiabetic agents or insulin, particularly during the first month of treatment with an ACE inhibitor.

Effects on Ability to Drive and Use Machines: Imidapril, like other antihypertensives, may cause dizziness or fatigue. Patients should exercise caution when driving vehicles or operating machinery.

INTERACTIONS WITH OTHER MEDICAMENTS

Potassium-sparing diuretics/potassium supplements/salt substitutes: May lead to significant increases in serum potassium. Use with caution and monitor serum potassium frequently.

Nonsteroidal anti-inflammatory drugs [NSAIDs, i.e., selective cyclooxygenase-2 inhibitors (COX-2) inhibitors, aspirin > 3 g/day]: Reduced antihypertensive effect of imidapril. Concurrent administration of ACE inhibitors and NSAIDs may result in an increased risk of worsening of renal function (including possible acute renal failure) and an increase in serum potassium, particularly in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Regularly monitor renal function after initiation of concomitant therapy and adequately hydrate patients.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS): Dual blockade of the RAAS with ACE inhibitors, angiotensin II receptor antagonists or aliskiren is associated with increased risk of hypotension, hyperkalemia and changes in renal function (including acute renal failure) compared with monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on imidapril and other agents that affect the RAAS.

Do not coadminister imidapril with aliskiren in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73 m^2). Avoid concomitant use of ACE inhibitors and angiotensin II receptor antagonists in patients with diabetic nephropathy.

Non-potassium-sparing diuretics: Risk of sudden hypotension and/or acute renal impairment. Discontinue the diuretic before initiating imidapril, or initiate with a lower dose of imidapril and increase progressively. The diuretic can be reintroduced thereafter. Monitor renal function during the first few weeks of therapy.

Lithium: May decrease lithium excretion leading to lithium toxicity. Monitor serum lithium levels frequently.

Antidiabetic agents (e.g., insulin, hypoglycemic agents): ACE inhibitors may increase the hypoglycemic effect in diabetic patients receiving insulin or hypoglycemic agents.
Tricyclic antidepressants, neuroleptics: Increased antihypertensive effect and risk of orthostatic hypotension

Rifampicin: May decrease the antihypertensive effect of imidapril

Antacids: May decrease imidapril bioavailability

Sympathomimetics: May decrease the antihypertensive effects of ACE inhibitors; patients should be carefully monitored to confirm that the desired effect is obtained.

Gold (sodium aurothiomalate): Nitroid reactions (including facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients receiving concomitant therapy with ACE inhibitor and injectable gold.

Other antihypertensive agents and vasodilators (e.g., nitroglycerin, nitrates): Increased blood pressure lowering effect of imidapril

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: ACE inhibitors should not be used during pregnancy. When pregnancy is diagnosed, immediately discontinue treatment with ACE inhibitors, and, if appropriate, alternative treatment should be started (see Warnings and Precautions, Fetal Toxicity).

Lactation: Imidapril, as with other ACE inhibitors, may be excreted in human milk. Discontinue breastfeeding or drug due to potential risk to breastfeeding infants, taking into consideration the importance of the drug to the mother.

Elderly: Imidapril is known to be excreted by the kidney, and the risk of adverse reactions to imidapril may be greater in patients with renal impairment. Care should be taken in dose selection since elderly patients are more likely to have decreased renal function.

Children: The safety and efficacy of imidapril in pediatric patients have not been established.

UNDESIRABLE EFFECTS

Infections and infestations: Viral infection

Blood and lymphatic system disorders: Agranulocytosis, thrombocytopenia, pancytopenia, anemia, leukopenia, neutropenia; individual cases of hemolytic anemia in patients with congenital deficiency of glucose-6-phosphate dehydrogenase (G6PD) have been reported with other ACE inhibitors

Metabolism and nutrition disorders: Hyperkalemia, hypoglycemia, thirst

Psychiatric disorders: Depression, sleep disorders, insomnia, sleepiness

Nervous system disorders: Dizziness, postural dizziness, somnolence, paresthesia, disorder of balance, confusion, headache, taste disturbance, lightheadedness, cerebral hemorrhage, cerebrovascular disorders

Eye disorders: Blurred vision

Ear and labyrinth disorders: Tinnitus

Cardiac disorders: Tachycardia, palpitations, arrhythmia, angina pectoris, myocardial infarction

Vascular disorders: Severe hypotension after initiation of therapy or increase of dose; dizziness, feeling of weakness, impaired vision, and disturbance of consciousness (syncope) can also occur in association with hypotension; transient ischemic attack, facial flushing

Respiratory, thoracic and mediastinal disorders: Cough, pharynx discomfort, hoarseness, dyspnea, sinusitis, rhinitis, glossitis, bronchitis, bronchospasm, upper respiratory tract infection, angioedema involving the upper airways, allergic alveolitis/eosinophilic pneumonia (very rare)

Gastrointestinal disorders: Diarrhea, nausea, queasy, vomiting, gastritis, abdominal pain, constipation, dry mouth, stomach discomfort, anorexia, ileus, pancreatitis, epigastric pain, dyspepsia, intestinal angioedema

Hepatobiliary disorders: Cholestatic icterus, hepatitis, jaundice

Skin and subcutaneous tissue disorders: Photosensitivity, allergic and hypersensitivity reactions such as rash, pruritus, exanthema, and urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pemphigus-like symptoms, psoriasis-like efflorescences, alopecia, cutaneous symptoms accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased antinuclear antibody (ANA) titers; angioneurotic edema involving the face and oropharyngeal tissues

Renal and urinary disorders: Renal impairment, acute renal failure, proteinuria, aggravation of renal function disorder

General disorders and administration site conditions: Feeling of weakness, numbness, fatigue, malaise, weariness, edema, chest discomfort, chest pain, pain in limbs

Reproductive system and breast disorders: Impotence

Investigations: Increases in blood urea nitrogen, plasma creatinine, serum potassium, liver enzymes, aspartate aminotrasnferase (AST), alanine aminotransferase, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (γ-GTP), serum bilirubin, creatine phosphokinase (CPK); decreases in erythrocyte, thrombocyte, leukocyte, hemoglobin, hematocrit, platelets, white blood cell count

OVERDOSE AND TREATMENT

Symptoms of overdosage with imidapril include severe hypotension, shock, stupor, bradycardia, electrolyte disturbances, and renal failure. After ingestion of an overdose, keep patient under close supervision, preferably in an intensive care unit. Monitor serum electrolytes and creatinine frequently. Measures to prevent absorption and hasten elimination such as gastric lavage, administration of adsorbents and sodium sulfate within 30 minutes after intake should be applied if ingestion is recent.
If hypotension occurs, place patient in the shock position and immediately give salt and volume supplementation. Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions may be treated with atropine. The use of a pacemaker may be considered.

Imidapril and imidaprilat may be removed from the circulation by hemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE CONDITIONS

Store at temperatures not exceeding 30°C.

Keep the product out of reach and sight of children.

Protect from moisture.

AVAILABILITY

Imidapril hydrochloride (Vascor®) 5 mg Tablet, in foil strip by 10's (Box of 100 tablets)
Imidapril hydrochloride (Vascor®) 10 mg Tablet, in foil strip by 10's (Box of 100 tablets)

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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Manufactured by AMHERST LABORATORIES, INC.
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Trusted Quality Healthcare

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