Imidapril hydrochloride

Vascor®

5 mg & 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.

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 tenfold increase in patients with creatinine clearance 10 to 29 mL/min.

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.

INDICATION	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 or any ACE inhibitor or any component of the product
- History of angioneurotic edema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Pregnancy
- Breastfeeding
- Renovascular hypertension
- Renal failure with or without hemodialysis

WARNINGS AND PRECAUTIONS

ACE inhibitors (e.g., imidapril) can cause injury and even death to the developing fetus when used in pregnancy during the second and third trimesters. Discontinue imidapril as soon as possible upon detection of pregnancy.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been observed, although it is not clear whether these occurrences were due to exposure to ACE inhibitors.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Discontinue imidapril as soon as possible when pregnancy is detected.

Infants with a history of *in utero* exposure to ACE inhibitors should be closely monitored 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. Imidapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

Hypotension: Imidapril, like other ACE inhibitors, may cause a profound fall in blood pressure particularly after the first dose. Symptomatic hypotension is rarely observed in patients with uncomplicated hypertension. Hypotension is more likely if the patient has been volume-depleted (e.g., by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting) in hypertensive patients given imidapril. 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: There are no data available on the use of imidapril in patients with 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.

Impaired Renal Function: 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 and 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. Symptoms usually appear within a few minutes after beginning hemodialysis. Consider giving a different type of dialysis membrane or a different class of antihypertensive agent in these patients.

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 occur during the first weeks of treatment. In rare cases, however, severe angioedema may develop after long term imidapril 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. Emergency therapy should be given including, but not necessarily limited to, immediate subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) or slow intravenous epinephrine 1 mg/mL (observe dilution instructions) with control of blood pressure and ECG. The patient should be hospitalized and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

Hypersensitivity to Insect Toxins, Insect Bites: When treated with an ACE inhibitor, patients with hypersensitivity to insect toxins who are undergoing desensitization treatment have an increased risk of severe anaphylactoid reactions. Discontinue imidapril before desensitization treatment. Similar reactions may occur after an insect bite in patients without known hypersensitivity to insect toxins.

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 was rarely observed with imidapril. Neutropenia may occur in patients with some degree of renal impairment, particularly when it is associated with a collagen vascular disease, e.g., systemic lupus erythematosus, scleroderma, and therapy with immunosuppressive agents. It is reversible after discontinuation of the ACE inhibitor.

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: Hyperkalemia has been rarely reported in some patients receiving imidapril, particularly in the presence of renal insufficiency and/or cardiac failure. 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)

INTERACTIONS WITH OTHER MEDICAMENTS

Potassium salts, Potassium-sparing diuretics, Potassium supplements: May lead to significant increases in serum potassium. Use with caution and monitor serum potassium frequently if concomitant use is necessary due to hypokalemia.
Diuretics: Excessive blood pressure reduction. The possible blood pressure lowering effect may be reduced by discontinuing the diuretic, increasing volume or salt intake prior to diuretic intake, and initiating therapy with a lower dose of imidapril.
Antihypertensive agents: Increased blood pressure lowering effect of ACE inhibitors
Lithium: May decrease lithium excretion leading to lithium toxicity. Monitor serum lithium levels frequently.
Anesthetic drugs: May enhance the hypotensive effects of certain anesthetic drugs
Narcotic drugs/Antipsychotics: Postural hypotension may occur
Allopurinol: Data from other ACE inhibitors indicate an increased risk of leukopenia
Cytostatic or Immunosupressive agents, Systemic corticosteroids or Procainamide: May lead to an increased risk of leukopenia
Nonsteroidal anti-inflammatory drugs (NSAIDs): May reduce the antihypertensive effect of ACE inhibitors, increase serum potassium, and decrease renal function
Rifampicin: May decrease the antihypertensive effect of imidapril
Antidiabetics (e.g., insulin, oral hypoglycemic agents): ACE inhibitors may enhance insulin sensitivity. As a consequence, symptomatic hypoglycemia may occur in patients concomitantly receiving insulin or oral antidiabetics and 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.
Alcohol: May enhance the hypotensive effect of ACE inhibitors

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/Neonatal Morbidity and Mortality**).

LACTATION: Imidapril, as with other ACE inhibitors, may be excreted in breast milk; its effect on the breast-fed infant has not been determined.

GERIATRICS: 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 children have not been established.

UNDESIRABLE EFFECTS

General: Feeling of weakness, numbness, fatigue, malaise, edema, facial flushing
Cardiovascular: 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; tachycardia, palpitations, arrhythmias, angina pectoris, myocardial infarction, transient ischemic attacks, cerebral hemorrhage, chest discomfort
Gastrointestinal: Diarrhea, nausea, queasy, vomiting, gastritis, abdominal pain, constipation, dry mouth, cholestatic icterus, hepatitis, pancreatitis, ileus, jaundice, stomach discomfort, anorexia, thirst
Metabolic: Hypoglycemia
Nervous: Occasionally, dizziness, weariness, fatigue, somnolence; rarely, depression, sleep disorders, insomnia, sleepiness, paresthesias, impotence, disorder of balance, confusion, tinnitus, blurred vision, headache, taste disturbance, lightheadedness
Renal: Renal insufficiency (rare), acute renal failure, aggravation of renal function disorder, proteinuria
Respiratory: Cough, pharynx discomfort, hoarseness; rarely, dyspnea, sinusitis, rhinitis, glossitis, bronchitis, bronchospasm and angioedema involving the upper airways, and very rarely, allergic alveolitis/eosinophilic pneumonia
Skin: Itching, photosensitivity; rarely, allergic and hypersensitivity reactions such as rash, pruritus, exanthema, and urticaria; cases of erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythroderma, pemphigus-like symptoms, psoriasis-like efflorescences, alopecia; cutaneous symptoms accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased antinuclear antibody (ANA) titers; onset of angioneurotic edema involving the face and oropharyngeal tissues
Special senses: Tinnitus
Other adverse effects: Increases in blood urea and plasma creatinine may occur, especially in the presence of renal insufficiency. This is reversible upon drug discontinuation. Elevation of serum potassium can occur since imidapril leads to decreased aldosterone secretion. Other reported adverse effects are decreases in erythrocyte, hemoglobin, hematocrit, platelets, and white cell count as well as increases in liver enzymes, aspartate aminotrasnferase (AST), alanine aminotransferase, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (γ-GTP), serum bilirubin and creatine phosphokinase (CPK). Agranulocytosis, thrombocytopenia, or pancytopenia may also occur. Individual cases of hemolytic anemia in patients with congenital deficiency of G-6-PDH have been reported with other ACE inhibitors.

OVERDOSE AND TREATMENT

Symptoms of overdosage 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.

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

STORAGE CONDITION
Store at temperatures not exceeding 30°C
Keep the product out of sight and reach of children
Protect from moisture

AVAILABILITY
Vascor® 5 mg Tablet in flex foil of 10 (Box of 100 tablets)
Vascor® 10 mg Tablet in flex foil of 10 (Box of 100 tablets)

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