EN-2436

Enalaprilat Injection, USP

Hospira, Inc., Lake Forest, IL 60045 USA

Revised: March, 2010

USUPPLIED

***Registered trademark of B. Braun Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

ber Box -im/6m 25. Quantity 1111 Concentration Container Enalaprilat Injection, USP 1.25 mg per mL, is a clear, colorless solution and is supplied as follows:

> 0.9 percent Sodium Chloride Injection in 5 percent Dextrose 5 percent Dextrose in Lactated Ringer's Injection B. Braun ISOLYTE***E activity for 24 hours at room temperature: 5 percent Dextrose Injection 0.9 percent Sodium Chloride Injection

Enalaprilat Injection as supplied and mixed with the following intravenous diluents has been found to maintain full nspected visually for particulate matter and discoloration prior to use whenever solution and container peri Sompatibility and Stability

Enalaprilat Injection should be administered as a slow intravenous infusion, as indicated above. It may be administered as provided or diluted with up to 50 mL of a compatible dilutent. Parenteral drug products should be Patients should be followed closely whenever the dose of enalaprilat is adjusted and/or diuretic is increased.

started under very close medical supervision. The starting dose should be no greater than 0.825 mg administered intravenously overs a pent of no less that interminister and prefer help from the found. Progress is extracted to the contract should be followed closely uneared to the contract should be followed closely uneared to the contract should be followed closely uneared to the contract of the diagnoses. Because of the potential for an extreme hypotensive response in these patients, therapy should be diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology (see **WARNINGS**). Single doses of enalaprilat as low as 0.2 mg have produced excessive hypotension in normotensive patients with these Hypertensive patients at risk of excessive hypotension include those with the following concurrent conditions or consecutations; heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in Patients at Risk of Excessive Hypotension

For conversion from intravenous to oral therapy, the recommended initial dose of Enalapril Maleate Tablets is 5 mg once a day for patients with creatinine clearance >30 mL/min and 2.5 mg once daily for patients with creatinine clearance should then be adjusted according to blood pressure response. Patients at Bisly the *Presessing Hundensign If after one hour there is an inadequate clinical response, the 0.625 mg dose may be repeated. Additional doses of 1.25 mg may be administered at six hour intervals. For dialysis patients, see below, **Patients at Risk of Excessive Hypotension**.

The usual dose of 1.25 mg of enalgaprilat every six hours is recommended for patients with a creatinine clearance \$30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance \$30 mL/min serum creatinine \$3 mg/dL), the initial dose is 0.50m 7.00m (\$60 mL/min) and the companion of the property o Dosage Adjustment in Renal Impairment ozade adjustment as necessary

oatients who have responded to 0.625 mg of enalaprilat every six hours is 2.5 mg once a day with subsequent For conversion from intravenous to oral therapy, the recommended initial dose of Enalapril Maleate Tablets for

clinical response, the 0.625 mg dose may be repeated. Additional doses of 1.25 mg may be administered at six hour of Enalapril Maleate Tablets is 5 mg once a day with subsequent dosage adjustments as necessary.

Patients on Diuretic Therapy.

Patients on Diuretic Therapy.

48 hours. In other studies, patients have received enalaprilat injection for as long as seven days.
The dose for patients being converted to enalaprilat injection from oral therapy for hypertension with enalapril maleate is 1.25 mg every six hours. For conversion from intravenous to oral therapy, the recommended initial dose greater than 20 mg per day. In studies of patients with hypertension, enalaprilat injection has not been administered for periods longer than

as 5 mg every six hours were well tolerated for up to 36 hours. There has been inadequate experience with doses dosing. The peak effects of the second and subsequent doses may exceed those of the first. No dosage regimen for enalaprilat injection has been clearly demonstrated to be more effective in treating hypertension than 1.25 mg every six hours. However, in controlled clinical studies in hypertension, doses as high

FOR INTRAVENDUS ADMINISTRATION ONLY
The dose in hypertension is 1.25 mg every six hours administered intravenously over a five minute period. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after

The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous intuition of normals saline solution.

Enalaptilat may be removed from general circulation by hemodialysis and has been removed from neonatal circulation by peritoneal dialysis. (See WARNINGS, Anaphylactoid Reactions During Membrane Exposure.)

BOSAGE AND ADMINISTRATION

BOSAGE AND ADMINISTRATION

A single intravenous dose of ≤4167 mg/kg of enalaprilat was associated with lethality in female mice. Molethality ccurred after an intravenous dose of 3472 mg/kg. dosages were observed. In clinical studies, some hypertensive patients received a maximum dose of 80 mg of enalaprilat intravenously over a fifteen minute period. At this high dose, no adverse effects beyond those as associated with the recommended as fifteen minute period.

Concomination directed of the decreases of approximately sentences of supproximately the decreases of approximately the decreases of approximately form and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with enalghril but 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with enalghril but of percent and 1.0 vol percent and 1.0 vol percent of percent, respectively due to anemia. Hemolytic anemia, including cases of hemolysis in patients with of periods disciency, has been reported; a causal relationship to enalapril cannot be excluded. Liver function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, Hepatic Elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, Hepatic

Ungenital: Genal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), unitary tract infection, flank pain, ylnecoemastia, impotence.

Miscellaneous: A symptom complex has been reported which may include some or all of the following: a positive Miscellaneous: A symptom complex has been reported which may include some or all of the following: a positive, has nelevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, photoprension or congestive heart failure, hypotension including postural hypotension, and other orthostatic effects, was reported in 2.3 percent of patients. Hypotension or congestive heart failure, following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension or congestive has a cause for discontinuation of therapy in 0.1 percent of hypertensive patients. (See WARNINGS.)

Clinical Laboratory Test Findings

Creation of therapy in 0.1 percent of hypertensive patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1 percent of patients. Hypotension or syncope was a cause for clinical Laboratory Test Findings

Clinical Laboratory Test Findings

Creation of therapy in 0.1 percent of patients. Hypotension or syncope was a cause for secured in 0.9 percent and syncope occurred in 0.9 percent and syncope occurred in 0.9 percent of patients. Hypotension of therapy, not occurred in 0.9 percent of patients with creatishe upon discontinuation of therapy, were observed in about 0.2 percent of patients with escaping with enalar effects are more likely to occur in patients ereceiving essential the patients of the patients of perceiving the patients of the patients of perceiving the patients of the patients of perceiving the patients of a paproximately hematology. Small decreases of approximately thematology small decreases of approximately

Muceuloskeletel: Muscle Gramps.

Mervous/Psychiatry Depression, vertigo, confusion, ataxia, somnolence, insomnia, nervousness, peripheral neuropatry (e.g., peressinesia, dyseathesia), dream abnormality.

neuropatry (e.g., peresthesia, dyseathesia), dream abnormality, cough, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, pulmonary infiltrates, eosinophilic pneumonits.

Skint: Extoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigus, herpes zoster, Skeria etmantitiorme, urticaria, pruntus, alopecia, flushing, diaphoresis, photosensitivity.

Skint: Extoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigus, herpes zoster, Skeria Stevens-Johnson syndrome, pemphigus, herpes zoster, skerial senses: Blurred vision, taste alteration, anoranis, tinnifus, conjunctivitis, dry eyes, tearing.

Urogenital: Renal staliute, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), urinary tract infection, flank pain, gynecomastia, impotence.

Hematologic: Rare cases of neutropenia, thrombocytopenia and bone marrow depression.

pulmonary edema; rhythm disrurbances including atrial tachycardia and bradycardia; atrial fibrillation; orthostatic Mypotanson; angina pectoris; palpitation; hapatita (hepaticaellular (proven on rechallenge) or cholestatic Digestive: lleus, pancreatità, hepatic failure), melena, diarrhea, vomiting, dyspepsia, anorexia, glossitis, stomatitis, jaundice) (see WARNINGS, Hepatic Failure), melena, diarrhea, vomiting, dyspepsia, anorexia, glossitis, stomatitis, order of decreasing severity.

Body As. A Whole: Syncope, orthostatic effects, anaphylactoid reactions (see WARNINGS, Anaphylactoid Body As. A Whole: Syncope, orthostatic effects, anaphylactoid reactions (see WARNINGS, Arghenia).

Cardiovascular: Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to sexessive hypotension in high risk patients (see WARNINGS, Hypotension); pulmonary embolism and infarction; purpotension in high risk patients (see WARNINGS, Hypotension); pulmonary embolism and infarction; pulmonary enhants, my site and process including arisk attachments.

The following adverse experiences have been reported with enalapril and, within each category, are listed in Since enalapril is converted to enalaprilat, those adverse experiences associated with enalapril might also be expected to occur with Enalaprilat Injection.

The distinct associated with Enalaprilat Injection. Cough: See PRECAUTIONS, Cough

(i.r.) percent, converse experiences occurring in 0.5 to 1.0 percent of patients in controlled clinical trials included; myocardial infarction, fatigue, disziness, fever, rash and constipation. Adigloedems Angioedems has been reported in patients receiving enalaphilat, with an incidence higher in black than in non-black patients. Angioedems associated with laryngeal edems may be fatal. If angioedems of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with enalaphilat should be discontinued and extremities, lips, tongue, glottis and/or larynx occurs, treatment with enalaphilat should be discontinued and conditions.

doctse experiences occurring in greater than one percent of patients were; headache (2.9 percent) and nausea Enalaphrilat Injection has been found to be generally well tolerated in controlled clinical trials involving 349 patients (368 with hypertension, 153 with congestive heart failure and 28 with coronary artery disease). The most frequent (clinically significant adverse experience was hypertension (34 percent), orccurring in eight patients (5.2 percent) with hypertension and one with coronary artery disease. Other with coronary artery disease. Other adverse experiences occurring in enterent land may be adverse experience or transfer one one may be adversed to the control of the coronary artery disease.

ADVERSE REACTIONS This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function. Evaluation of the hypertensive patient should always include function, care should be taken in dose selection. Evaluation of the hypertensive patient should always include assessment of renal function. (See **DOSAGE AND ADMINISTRATION.**)

Clinical studies of Enaleprilat Injection did not include sufficient numbers of subjects aged 65 and over to determine Whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosting range, reflecting the greater frequency of decreased lepatic, renal, or cardiac function, and of concomitant disease or other drug therepty.

satety and effectiveness in pediatric patients have not been established.

discontinue Enalaprilat Injection, taking into account the importance of the drug to the mother. Nursing Mothers

Enalapril and enalaprilat have been detected in human breast milk. Because of the potential for serious adverse reactions in nursing infants from enalapril, a decision should be made whether to discontinue nursing or to

Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, Fetal/Neonatal Morbidity and Mortality. dilace area basis).

Enalsprilst Injection was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalsprilst browed no drug-related changes in the following genotoxicity studies: recesses, the everse mutablion assay, with £ colf, sister chromatid exchange with cultured mammalian cells, the micronucleus fest with mice, and in an in vivo cytogenic study using mouse bone marrow. There were no adverse effects on reproductive performance of male and at manile and female rats treated with up to 90 mg/kg/day of enalspril (26 times the MRHDD when compared on a body surface area have.)

dose (MKHDD) when compared on a body surface area basis. 90 mg/kg/day or for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively. These doses are 25 times (in rats and female mice) and 12 mass (in maximum recommended human daily doses are 26 times (in rats and female mice) and 12 mass (in maximum recommended human daily doses are 26 maximum recommended human daily Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been done with Enalaprilat Injection.
Enalaprilat Injection is the bioactive form of its eithyl ease, enalapril maleate. There was no evidence of a tunnoriganic effect when enalapril was administered for 106 weeks to male and female rats at doses up to 400 monthly of the contract of the contract of the contract of the weeks to male and female rate at doses up to 400 monthly of the contract of the contract

ecommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with Lithium Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients elimination of sodium, including the properties of the concomitant enables in the concomitant enables. The concomitant enables in the concomitant properties of the concomitan

caution and with frequent monitoring of serum potassium. potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of three pents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent montroring of serum potassium aiuretics. Potassium-sparing aiuretics (e.g., spironoiactone, triamterene, or amiloride), potassium supplements, or interaction should be given consideration in patients taking MSAIDs concomitantly with ACE inhibitors. Other Cardiovasculiar Agents: Enalapirilar Injection has been used concomitantly with digitalis, beta advence; blocking agents, methylops, interescions. evidence of clinically significant adverse interactions. Agents Increasing Serum Polassuum. Loss caused by thiazide-type Agents Increasing Serum Polassuum. Enalapirilar Infection attenuates potassuum loss caused by thiazide-type interescions. Polassuum since and programments or since the amount of the control of the c maleate. However, reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This

Enalaprilat Injection, USP

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Enalaprilat Injection, USP should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Enalaprilat Injection, USP is a sterile aqueous solution for intravenous administration. Enalaprilat is an angiotensin converting enzyme inhibitor. It is chemically described as (S)-1-[N-(1-carboxy-3-phenylpropyl)-L-alanyl]-L-proline dihydrate. Its molecular formula is $C_{18}H_{24}N_2O_5 \circ 2H_2O$ and its structural formula is:

Enalaprilat is a white to off-white, crystalline powder with a molecular weight of 384.43. It is sparingly soluble in methanol and slightly soluble in water.

Each milliliter contains 1.25 mg enalaprilat (anhydrous equivalent); sodium chloride to adjust tonicity; benzyl alcohol, 9 mg, added as a preservative. May contain sodium hydroxide for pH adjustment. CLINICAL PHARMACOLOGY

Enalaprilat, an angiotensin-converting enzyme (ACE) inhibitor when administered intravenously, is the active metabolite of the orally administered pro-drug, enalapril maleate. Enalaprilat is poorly absorbed orally

Intravenous enalaprilat, or oral enalapril, after hydrolysis to enalaprilat, inhibits ACE in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalapril alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril plus a thiazide diuretic, there was essentially no change in serum potassium. (See *PRECAUTIONS*.) Removal of angiotensin II negative feedback on renin secretion leads to ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a

potent vasodepressor peptide, play a role in the therapeutic effects of enalaprilat remains to be elucidated.

While the mechanism through which enalaprilat lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalaprilat has antihypertensive activity even in patients with low-renin hypertension. In clinical studies, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalaprilat monotherapy than non-black patients. Pharmacokinetics and Metabolism

Following intravenous administration of a single dose, the serum concentration profile of enalaprilat is polyexponential with a prolonged terminal phase, apparently representing a small fraction of the administered dose that has been bound to ACE. The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalaprilat, as determined from oral administration of multiple doses of enalapril maleate, is approximately 11 hours. Excretion of enalaprilat is primarily renal with more than 90 percent of an administered dose recovered in the urine as unchanged drug within 24 hours. Enalaprilat is poorly absorbed

following oral administration.

The disposition of enalaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate ≤30 mL/min, peak and trough enalaprilat levels increase, time to peak concentration increases and time to steady state may be delayed. The effective half-life of enalaprilat is prolonged at this level of renal insufficiency. (See **DOSAGE AND ADMINISTRATION**.) Enalaprilat is dialyzable at the rate of 62 mL/min.

Studies in dogs indicate that enalaprilat does not enter the brain, and that enalapril crosses the blood-brain barrier poorly, if at all. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk in lactating rats contains radioactivity following administration of ¹⁴C enalapril maleate. Radioactivity was found to cross the placenta following administration of labeled drug to pregnant hamsters. Pharmacodynamics
Enalaprilat Injection results in the reduction of both supine and standing systolic and diastolic blood pressure,

usually with no orthostatic component. Symptomatic postural hypotension is therefore infrequent, although it might be anticipated in volume-depleted patients (see **WARNINGS**). The onset of action usually occurs within fifteen minutes of administration with the maximum effect occurring within one to four hours. The abrupt withdrawal of enalaprilat has not been associated with a rapid increase in blood pressure.

The duration of hemodynamic effects appears to be dose-related. However, for the recommended dose, the duration of action in most patients is approximately six hours.

Following administration of enalapril, there is an increase in renal blood flow; glomerular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril maleate. In this study there was no evidence of a blunting of the antihypertensive action of enalapril maleate. PRECAUTIONS Drug hypertensive. maleate (see PRECAUTIONS, Drug Interactions).

INDICATIONS AND USAGE

INDICATIONS AND USAGE
Enalaprilat Injection is indicated for the treatment of hypertension when oral therapy is not practical.

Enalaprilat Injection has been studied with only one other antihypertensive agent, furosemide, which showed approximately additive effects on blood pressure. Enalapril, the pro-drug of enalaprilat, has been used extensively with a variety of other antihypertensive agents, without apparent difficulty except for occasional hypotension. In using Enalaprilat Injection, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that Enalaprilat Injection does not have a similar risk (See WARNINGS). risk. (See WARNINGS.)

In considering use of Enalaprilat Injection, it should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, Angioedema.)

CONTRAINDICATIONS Enalaprilat Injection is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inh and in patients with hereditary or idiopathic angioedema.

WARNINGS

Excessive hypotension is rare in uncomplicated hypertensive patients but is a possible consequence of the use of enalaprilat especially in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis. Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic, reduce the diuretic dose or increase salt intake cautiously before initiating therapy with Enalaprilat Injection in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See *PRECAUTIONS*, **Drug Interactions**, *ADVERSE REACTIONS*, and *DOSAGE AND ADMINISTRATION*.) In patients with heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential for an excessive fall in blood pressure especially in these patients, therapy should be followed closely whenever the dose of enalaprilat is adjusted and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an

intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including Enalaprilat Injection) may be subject to a variety of adverse reactions, some of them serious.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalaprilat. This may occur at any time during treatment. In such cases, Enalaprilat Injection should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or laryn, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided. (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

Anaphylactoid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon

Anaphylactoid Reactions During Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis in similar rates. Marketing experience has revealed cases of neutropenia, or agranulocytosis in which a causal relationship to enalapril cannot be excluded.

eriodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should 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. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be

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 reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimpster Mothers whose ambrous and fatures are exposed to ACE inhibitors only during the first.

limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of Enalaprilat Injection as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, Enalaprilat Injection should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal parfision. Exphanage transfission or dialysis may be required as means of reparsing hypotension and/or substituting.

perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, 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,

No teratogenic effects of oral enalapril were seen in studies of pregnant rats and rabbits. On a body surface area basis, the doses used were 57 times and 12 times, respectively, the maximum recommended human daily dose (MRHDD).

PRECAUTIONS

Acrtic Stenosis/Hypertrophic Cardiomyopathy. As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril or enalaprilat, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients receiving enalapril. These increases were almost always reversible upon discontinuation of enalapril or enalaprilat and/or diuretic therapy. In such

patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalaprilat has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalaprilat and/or discontinuation of the diuretic may be required. on of the hypertensive patient should always include assessment of renal function. (See *DOSAGE AND*

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials receiving enalapril. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing agents or potassium supplements, which should be used cautiously, if at all,

with Enalaprilat Injection. (See **Drug Interactions**).

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

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin Il formation secondary to compensatory reinir clease. If hypotension course and its persistence of the during anesthesia with agents that produce hypotension, enalapril may block angiotensin Il formation secondary to compensatory reinir clease. If hypotension course and its persistence of the during a persistent business and a personal business are presented by a personal production.

occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. Orug Interactions

Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported

rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy. Hypotension—Patients on Diuretic Therapy. Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalaprilat. The possibility of hypotensive effects with enalaprilat can be minimized by administration of an intravenous infusion of normal saline, discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalaprilat. If it is necessary to continue the diuretic, provide close medical supervision for at least one hour after the initial dose of enalaprilat. (See **WARNINGS**.)

Agents Causing Renin Release: The antihypertensive effect of Enalaprilat Injection appears to be augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of enalapril may result in a further deterioration of renal function. These effects are usually reversible.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril maleate. In this study there was no evidence of a blunting of the antihypertensive action of enalapril

Last Time Saved: 3/8/10 2:36 PM Document Name: QEN-2436v3.qxp PMS Black