

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204308Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPANED safely and effectively. See full prescribing information for EPANED.

EPANED™ (enalapril) for Oral Solution

Initial U.S. Approval: 1985

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- When pregnancy is detected, discontinue EPANED as soon as possible. (5.1)
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)

INDICATIONS AND USAGE

EPANED is an angiotensin-converting enzyme inhibitor indicated for:

- treatment of hypertension in adults and children older than one month, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. (1.1)

DOSAGE AND ADMINISTRATION

Hypertension

- Adult: recommended initial dose is 5 mg once daily. (2.1)
- Pediatrics: recommended starting dose is 0.08 mg/kg (up to 5 mg) once daily. (2.3)

The maximum dose is 40 mg/day (adults). (2.2)

DOSAGE FORMS AND STRENGTHS

EPANED Powder for Oral Solution contains 150 mg of enalapril maleate in a 150 mL bottle. Reconstitution with 150 mL of ORA-SWEET® SF provided results in a 1 mg/mL EPANED oral solution. (3)

CONTRAINDICATIONS

- Hypersensitivity related to previous treatment with an ACEI. (4)
- Hereditary or idiopathic angioedema. (4)
- Do not co-administer aliskiren in patients with diabetes. (4)

WARNINGS AND PRECAUTIONS

- Angioedema and Anaphylactoid Reactions. (5.2)
- Impaired Renal Function: Assess renal function. (5.5)
- Hyperkalemia. (5.6)

ADVERSE REACTIONS

In patients with hypertension, adverse reactions were uncommon. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Silvergate Pharmaceuticals at 1-855-379-0383 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- In patients who are elderly, volume-depleted (as on diuretic therapy), or with compromised renal function, use with NSAIDs, including selective COX-2 inhibitors, may result in deterioration of renal function, including renal failure. Monitor renal function periodically. (7.1)
- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension and hyperkalemia. (7.2)
- Avoid potassium sparing agents in patients with heart failure. (7.3)
- Monitor serum lithium levels frequently. (7.4)

USE IN SPECIFIC POPULATIONS

- EPANED is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 mL/min/1.73m². (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2013

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FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue EPANED™ as soon as possible.**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. [See Warnings and Precautions (5.1)]**

1 INDICATIONS AND USAGE

1.1 Hypertension

EPANED is indicated for the treatment of hypertension, to lower blood pressure in adults and children older than one month.

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including this drug.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects

(e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

EPANED is effective alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of EPANED and thiazides are approximately additive.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

Adults: The recommended initial dose in adults is 5 mg once a day. Titrate upward to maximum of 40 mg daily as needed to help achieve blood pressure goals. The dose may be divided and administered twice daily if the antihypertensive effect diminishes at the end of the dosing interval.

Use with diuretics: If additional blood pressure reduction is needed, EPANED may be administered with a low dose of diuretic. The recommended initial dose in patients taking diuretics is 2.5 mg daily.

Dosage Adjustment for Renal Impairment: See table below. The dosage may be titrated upward as needed to a maximum of 40 mg daily.

Renal Status	Creatinine-Clearance mL/min	Initial Dose mg/day
Normal or Mild Impairment of Renal Function	>30 mL/min	5 mg
Moderate to Severe Impairment	≤30 mL/min	2.5 mg
Dialysis Patients*	–	2.5 mg on dialysis days†

* = [See Warnings and Precautions (5.2)].
† = Dosage on nondialysis days should be adjusted depending on the blood pressure response.

Children >1 month: The usual recommended starting dose is 0.08 mg/kg (up to 5 mg) once daily. Dosage should be adjusted according to blood pressure response. Doses above 0.58 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients [see *Clinical Pharmacology (12.3)*].

EPANED is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m², as no data are available.

2.2 Preparation of EPANED (for 150 mL, 1 mg/mL enalapril solution)

EPANED Powder for Oral Solution is a kit containing 1 bottle of enalapril powder and 1 bottle of Ora-Sweet SF diluent to be added to the enalapril powder prior to dispensing to the patient.

Firmly tap the EPANED Powder for Oral Solution bottle on a hard surface 5 times. Add approximately one-half (75 mL) of the Ora-Sweet SF diluent to the 150 mL EPANED Powder for Oral Solution bottle. Replace the child-resistant cap. Shake well for 30 seconds. Reopen. Add the remainder of the Ora-Sweet SF diluent to the EPANED Powder for Oral Solution bottle, replace the child-resistant cap and shake well for an additional 30 seconds. Calculate 60 days from the date of reconstitution. Write this date as the discard date on the front of the label. Affix a “Do Not Use After” or a “Discard After” label with the calculated date added to the reconstituted EPANED bottle.

3 DOSAGE FORMS AND STRENGTHS

EPANED Powder for Oral Solution is a kit that contains 150 mg of enalapril maleate powder in a 150-mL bottle and Ora-Sweet SF diluent. Reconstitution with 150 mL of the provided Ora-Sweet SF diluent results in a 1 mg/mL EPANED oral solution.

4 CONTRAINDICATIONS

EPANED is contraindicated in patients with:

- a history of angioedema or hypersensitivity related to previous treatment with an angiotensin converting enzyme (ACE) inhibitor [*see Warnings and Precautions 5.2*]
- hereditary or idiopathic angioedema [*see Warnings and Precautions 5.2*]

Do not co-administer aliskiren with EPANED in patients with diabetes [*see Drug Interactions (7.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Pregnancy Category D

Use of drugs that act on the renin-angiotensin 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 EPANED as soon as possible [*see Use in Specific Populations (8.1)*].

5.2 Angioedema and Anaphylactoid Reactions

Head and Neck Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx, including some fatal reactions, have occurred in patients treated with angiotensin converting enzyme inhibitors, including EPANED, at any time during treatment. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. EPANED should be promptly discontinued and appropriate therapy and

monitoring should be provided until complete and sustained resolution of signs and symptoms of angioedema has occurred.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor [*see Contraindications (4)*]. ACE inhibitors have been associated with a higher rate of angioedema in black than in non-black patients.

Intestinal Angioedema

Intestinal angioedema has occurred in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. In some cases, the angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor.

Anaphylactoid Reactions during Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions.

Anaphylactoid Reactions during Dialysis

Sudden and potentially life-threatening anaphylactoid reactions have occurred in some patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions must be initiated. Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

5.3 Hypotension

EPANED can cause symptomatic hypotension, sometimes complicated by oliguria, progressive azotemia, acute renal failure or death. Patients at risk of excessive hypotension include those with the following conditions or characteristics: heart failure with systolic blood pressure below 100 mmHg, ischemic heart disease, cerebrovascular disease, hyponatremia, high dose diuretic therapy, renal dialysis, or severe volume and/or salt depletion of any etiology.

In these patients, EPANED should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of EPANED and/or diuretic is increased.

Symptomatic hypotension is also possible in patients with severe aortic stenosis or hypertrophic cardiomyopathy.

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, EPANED may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be through this mechanism, it can be corrected by volume expansion.

5.4 Hepatic Failure

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 inhibitor and receive appropriate medical follow-up.

5.5 Impaired Renal Function

Monitor renal function in patients treated with EPANED. Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, post-myocardial infarction or volume depletion) may be at particular risk of developing acute renal failure on EPANED. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on EPANED [*see Adverse Reactions (6.2), Drug Interactions (7.2, 7.3)*].

5.6 Hyperkalemia

Serum potassium should be monitored in patients receiving EPANED. Drugs that inhibit the renin angiotensin system can cause hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes [*see Drug Interactions (7.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere:

- Angioedema [*see Warnings and Precautions (5.2)*]
- Hypotension [*see Warnings and Precautions (5.3)*]
- Hepatic failure [*see Warnings and Precautions (5.4)*]
- Renal impairment [*see Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Enalapril has been evaluated for safety in more than 10,000 patients, including over 1,000 patients treated for one year or more.

In clinical trials, discontinuation of therapy for clinical adverse experiences was required in 3.3% of patients with hypertension and in 5.7% of patients with heart failure.

Adverse reactions (where rate on enalapril exceeds the rate on placebo by at least 0.2%) occurring in greater than 1% of patients with hypertension treated with enalapril in controlled clinical trials are shown below. In patients treated with enalapril, the maximum duration of therapy was three years; in placebo treated patients, the maximum duration of therapy was 12 weeks.

Adverse Reactions Occurring in Greater Than 1% of Patients With Hypertension		
	Enalapril Maleate Tablets (n = 2314) Incidence (discontinuation)	Placebo (n = 230) Incidence
<i>Body As A Whole</i>		
Fatigue	3.0 (<0.1)	2.6
Orthostatic Effects	1.2 (<0.1)	0.0
Asthenia	1.1 (0.1)	0.9
<i>Respiratory</i>		
Cough	1.3 (0.1)	0.9
<i>Skin</i>		
Rash	1.4 (0.4)	0.4

6.2 Other Adverse Reactions from Clinical Studies or Postmarketing Experience

The following adverse reactions have been reported in clinical studies or postmarketing experience with enalapril. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5 to 1.0% of patients with hypertension or heart failure in clinical trials are listed below and, within each category, are in order of decreasing severity.

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients [*see Warnings and Precautions (5.3)*];

pulmonary embolism and infarction; pulmonary edema; rhythm disturbances, including atrial tachycardia and bradycardia; atrial fibrillation; palpitation; Raynaud's phenomenon.

Digestive: Ileus, pancreatitis, melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

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

Musculoskeletal: Muscle cramps.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, peripheral neuropathy (e.g., paresthesia, dysesthesia), dream abnormality.

Respiratory: Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, pulmonary infiltrates, eosinophilic pneumonitis.

Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigus, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, diaphoresis, photosensitivity.

Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

Urogenital: Flank pain, gynecomastia, impotence.

Miscellaneous: A symptom complex has been reported which may include some or all of the following: a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, dermatologic manifestations.

7 DRUG INTERACTIONS

7.1 Non-Steroidal Anti-Inflammatory Agents (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including enalapril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving enalapril and NSAID therapy.

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. However, reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors.

7.2 Dual Blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on EPANED and other agents that affect the RAS.

Do not co-administer aliskiren with EPANED in patients with diabetes. Avoid use of aliskiren with EPANED in patients with renal impairment (GFR <60 mL/min).

7.3 Agents Increasing Serum Potassium

EPANED attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium.

7.4 Lithium

Lithium toxicity has been reported in patients receiving enalapril and lithium concomitantly which was generally reversible. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

7.5 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 including enalapril.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Fetal Toxicity

Pregnancy Category D [*see Warnings and Precautions (5.1)*].

8.3 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 discontinue EPANED, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Neonates with a history of in utero exposure to enalapril maleate:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a 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, although there is no experience with the latter procedure.

Pediatric Patients 1 month to 16 years of age

Enalapril lowers blood pressure in hypertensive pediatric patients age 1 month to 16 years. Use of enalapril in these age groups is supported by evidence from adequate and well-controlled studies of enalapril in pediatric and adult patients as well as by published literature in pediatric patients [see *Clinical Pharmacology (12.3) and Dosage and Administration (2.3)*].

EPANED is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m², as no data are available.

10 OVERDOSAGE

Limited data are available in regard to overdosage in humans.

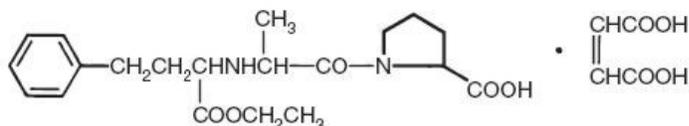
Single oral doses of enalapril above 1,000 mg/kg and $\geq 1,775$ mg/kg were associated with lethality in mice and rats, respectively.

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

Enalaprilat may be removed from general circulation by hemodialysis and has been removed from neonatal circulation by peritoneal dialysis.

11 DESCRIPTION

EPANED (Enalapril Maleate) Powder for Oral Solution is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin-converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1). Its empirical formula is C₂₀H₂₈N₂O₅•C₄H₄O₄, and its structural formula is:



Enalapril maleate is a white to off-white, crystalline powder with a molecular weight of 492.52. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol.

Enalapril is a pro-drug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin-converting enzyme inhibitor.

EPANED Powder for Oral Solution is a kit consisting of 1 bottle containing a dry powder blend of enalapril maleate, USP, mannitol, and colloidal silicon dioxide and 1 bottle of Ora-Sweet SF

diluent for reconstitution resulting in a 1 mg/mL EPANED oral solution. The Ora-Sweet SF diluent contains: purified water, glycerin, sorbitol, sodium saccharin, xanthan gum, and flavoring. Buffered with citric acid and sodium citrate. Preserved with methylparaben (0.03%), propylparaben (0.008%), and potassium sorbate (0.1%).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (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. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. 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 maleate tablets alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril maleate tablets plus a thiazide diuretic, there was essentially no change in serum potassium [*see Warnings and Precautions (5.6)*]. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

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 EPANED remains to be elucidated.

While the mechanism through which EPANED lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalapril is antihypertensive even in patients with low-renin hypertension. Although enalapril maleate tablets was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril monotherapy than non-black patients.

12.2 Pharmacodynamics

Adults

Administration of enalapril maleate tablets to patients with hypertension of severity ranging from mild to severe results in a reduction of both supine and standing blood pressure, usually with no orthostatic component. Symptomatic postural hypotension is therefore infrequent, although it might be anticipated in volume-depleted patients [*see Warnings and Precautions (5.3)*].

In most patients studied, after oral administration of a single dose of enalapril, onset of antihypertensive activity was seen at one hour with peak reduction of blood pressure achieved by four to six hours.

At recommended doses, antihypertensive effects have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval [*see Dosage and Administration (2.1)*].

In some patients achievement of optimal blood pressure reduction may require several weeks of therapy.

The antihypertensive effects of enalapril have continued during long-term therapy. Abrupt withdrawal of enalapril has not been associated with a rapid increase in blood pressure.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. 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.

When given together with thiazide-type diuretics, the blood pressure lowering effects of enalapril maleate are approximately additive.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril maleate tablets. In this study, there was no evidence of a blunting of the antihypertensive action of enalapril [*see Drug Interactions (7.1)*].

Pediatric Patients

In a clinical study involving 110 hypertensive pediatric patients 6 to 16 years of age, patients who weighed <50 kg received either 0.625, 2.5, or 20 mg of enalapril daily and patients who weighed ≥50 kg received either 1.25, 5, or 40 mg of enalapril daily. Enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive efficacy of enalapril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied, 0.625 mg and 1.25 mg, corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. In this study, enalapril maleate was generally well tolerated.

12.3 Pharmacokinetics

The pharmacokinetics of EPANED Oral Solution were shown to be similar to that of Vasotec[®] tablets under fasted conditions. A high-fat meal reduced the C_{max} of enalapril and enalaprilat by 46% and 36%, respectively. The exposure, as measured by AUC, to enalaprilat was reduced by 23%. The time to peak concentrations (C_{max}) was delayed by 20 minutes for enalapril and 62 minutes for enalaprilat. The trough plasma concentrations of enalapril (from 6 to 12 hours) and enalaprilat (from 16 to 36 hours) are similar between fasted and fed administrations.

Adults

Following oral administration of enalapril maleate tablets, peak serum concentrations of enalapril occur within about one hour. Based on urinary recovery, the extent of absorption of enalapril is approximately 60%. Enalapril absorption is not influenced by the presence of food in the

gastrointestinal tract. Following absorption, enalapril is hydrolyzed to enalaprilat, which is a more potent angiotensin-converting enzyme inhibitor than enalapril; enalaprilat is poorly absorbed when administered orally. Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of enalapril maleate. Excretion of enalapril is primarily renal.

Approximately 94% of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. There is no evidence of metabolites of enalapril, other than enalaprilat.

The serum concentration profile of enalaprilat exhibits 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 following multiple doses of enalapril maleate is 11 hours.

The disposition of enalapril and enalaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate is 30 mL/min or less. With 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 following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency [see *Dosage and Administration (2.2)*]. Enalaprilat is dialyzable at the rate of 62 mL/min.

Pediatric Patients

A multiple dose pharmacokinetic study was conducted in 40 hypertensive male and female pediatric patients aged 2 months to ≤ 16 years following daily oral administration of 0.07 to 0.14 mg/kg enalapril maleate. At steady state, the mean effective half-life for accumulation of enalaprilat was 14 hours and the mean urinary recovery of total enalapril and enalaprilat in 24 hours was 68% of the administered dose. Conversion of enalapril to enalaprilat was in the range of 63-76%. The overall results of this study indicate that the pharmacokinetics of enalapril in hypertensive children aged 2 months to ≤ 16 years are consistent across the studied age groups and consistent with pharmacokinetic historic data in healthy adults.

In the above pediatric study, enalapril maleate was given as tablets and for those children and infants who were unable to swallow tablets or who required a lower dose than is available in tablet form, enalapril was administered in a suspension formulation.

Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of ^{14}C -enalapril maleate. Radioactivity was found to cross the placenta following administration of labeled drug to pregnant hamsters.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to male and female rats at doses up to 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 26 times (in rats and female mice) and 13 times (in male mice) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an in vivo cytogenetic study using mouse bone marrow.

There were no adverse effects on reproductive performance of male and female rats treated with up to 90 mg/kg/day of enalapril (26 times the MRHDD when compared on a body surface area basis).

16 HOW SUPPLIED/STORAGE AND HANDLING

EPANED is supplied as a kit.

NDC 52652-1001-1

- One bottle containing 150 mg of EPANED (enalapril) Powder for Oral Solution in an HDPE bottle with child-resistant cap to provide 1 mg/mL final concentration after reconstitution.
- One bottle containing 150 mL of Ora-Sweet SF provided as the diluent for reconstitution.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Do not freeze.

Keep container tightly closed.

Protect from moisture.

17 PATIENT COUNSELING INFORMATION

• Pregnancy

Tell female patients of childbearing age about the consequences of exposure to EPANED during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

• Angioedema

Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin-converting enzyme inhibitors, including enalapril. Advise patients to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities,

eyes, lips, or tongue, or difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

- **Hypotension**

Caution patients to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, tell patients to discontinue the drug until they have consulted with the prescribing physician.

Tell patients that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; advise patients to consult with their physician.

- **Hyperkalemia**

Tell patients not to use salt substitutes containing potassium without consulting their physician.

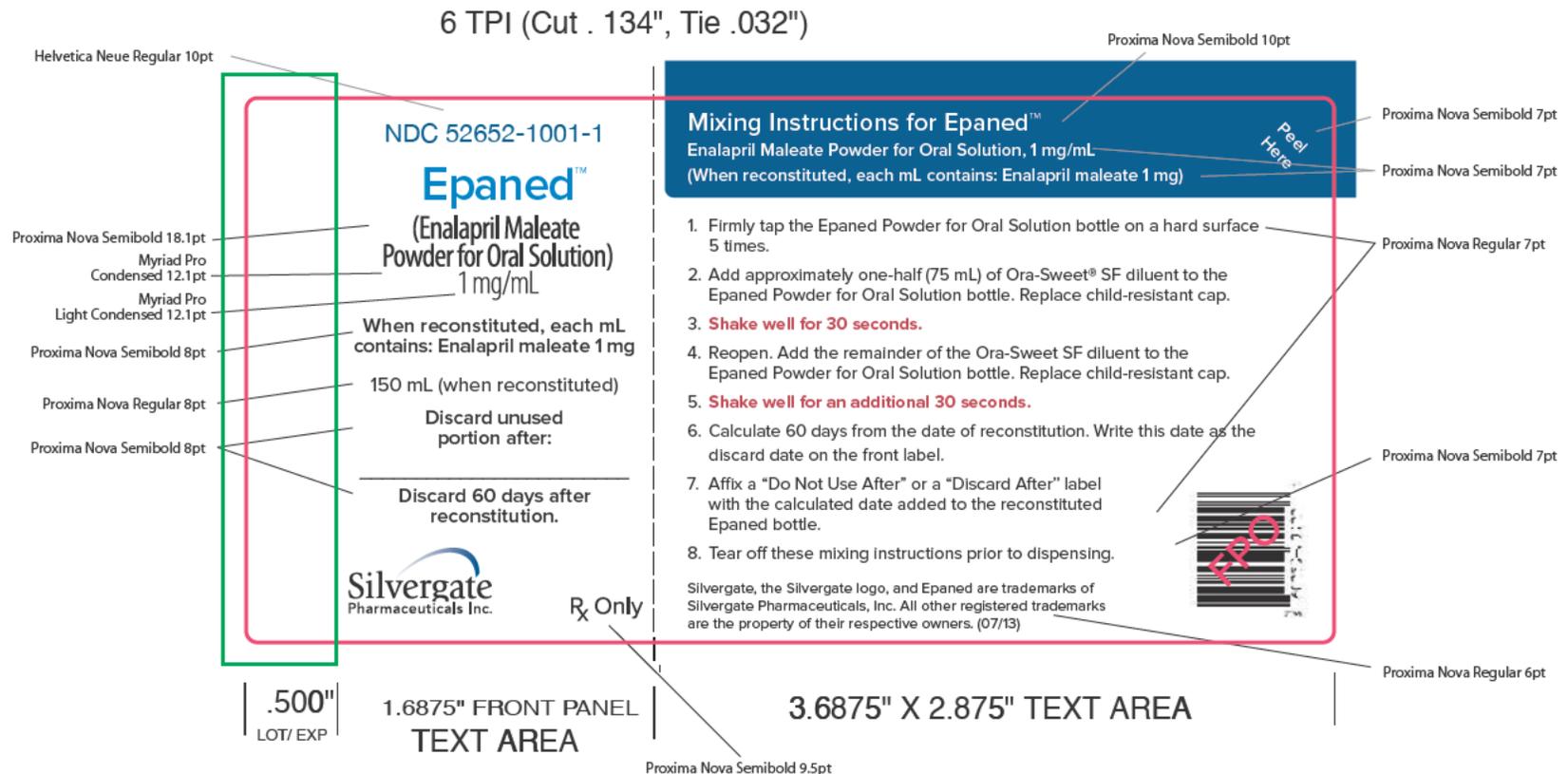
EPANED is a trademark of Silvergate Pharmaceuticals.

Manufactured For:
Silvergate Pharmaceuticals, Inc.
6251 Greenwood Plaza Blvd., Suite 101
Greenwood Village, CO 80111

EN-1304



Epaned Label –Top
revision date 7.12.13





Epaned Label–Bottom
revision date 7.12.13

6 TPI (Cut .134", Tie .032")

Store reconstituted solution at controlled room temperature, 15–30°C (59–86°F). [See USP Controlled Room Temperature] Do not freeze.

Discard 60 days after reconstitution.

Keep tightly closed.

**KEEP THIS AND ALL MEDICATIONS
OUT OF THE REACH OF CHILDREN**

Manufactured for:
Silvergate Pharmaceuticals, Inc.
6251 Greenwood Plaza Blvd, Suite 101
Greenwood Village, CO 80111



Proxima Nova Regular and Semibold 8pt

Silvergate, the Silvergate logo, and Epaned are trademarks of Silvergate Pharmaceuticals, Inc. All other registered trademarks are the property of their respective owners. (07/13)

Proxima Nova Regular 7pt

.500"
LOT/ EXP

1.6875" FRONT PANEL
TEXT AREA

3.6875" X 2.875" TEXT AREA



ORA-SWEET Label
revision date 7.11.13

6 TPI (Cut .134", Tie .032")

All copy here:
Proxima Nova Semibold/Regular 7pt

ORA-SWEET® SF

Citrus-Berry Flavor
Sugar-Free Syrup Vehicle

Diluent
for
Epaned™
(Enalapril Maleate
Powder for Oral Solution)
1 mg/mL

Net Contents
150 mL

CONTAINS: Purified water, glycerin, sorbitol, sodium saccharin, xanthan gum, and flavoring. Buffered with citric acid and sodium citrate. Preserved with methylparaben (0.03%), propylparaben (0.008%), and potassium sorbate (0.1%).

Directions for reconstituting Epaned™:

1. Firmly tap the Epaned Powder for Oral Solution bottle on a hard surface 5 times.
2. Add approximately one-half (75 mL) of the Ora-Sweet® SF diluent to the Epaned Powder for Oral Solution bottle. Replace child-resistant cap.
3. **Shake well for 30 seconds.**
4. Reopen. Add the remainder of the Ora-Sweet SF diluent to the Epaned Powder for Oral Solution bottle. Replace child-resistant cap.
5. **Shake well for an additional 30 seconds.**
6. Follow the remaining directions, steps 6–8, on the Epaned Powder for Oral Solution bottle.

Store at controlled room temperature, 15–30°C (59–86°F).
[See USP Controlled Room Temperature]

Keep Tightly Closed
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN
Manufactured by Perrigo
Minneapolis, MN 55427
2202858 Rev 07-13 A

No Varnish

FPO lot/exp

1.6875" FRONT PANEL
TEXT AREA

3.6875" X 2.875" TEXT AREA

.500"
LOT/EXP

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/s/

NORMAN L STOCKBRIDGE
08/13/2013