### Adverse Effects
In pre-approval efficacy studies, the most common side effects observed were dermal- and gastrointestinal-related. In a field study, adverse reactions reported by cat owners included licking/excessive grooming (3%), scratching treatment site (2.5%), salivation (1.7%), lethargy (1.7%), alopecia (1.3%), agitation/nervousness (1.2%), vomiting (1%), diarrhea (0.5%), eye irritation in 3 cats (0.5%), respiratory irritation (0.2%) and shaking/tremors (0.2%). All adverse reactions were self-limiting. The following adverse events were reported voluntarily during post-approval use of the product in foreign markets: application site reaction (hair loss, dermatitis, pyoderma, edema, and erythema), salivation, pruritus, lethargy, vomiting, diarrhea, dehydration, ataxia, loss of appetite, facial swelling, rear leg paralysis, seizures, hyperesthesia, twitching, and death.

### Reproductive/Nursing Safety
Safe use has not been evaluated in cats used for breeding, during pregnancy, or in lactating queens. Studies performed in laboratory animals (rats, rabbits suggest that emodepside may interfere with fetal development in those species.

### Overdosage/Acute Toxicity
Oral doses of emodepside of 200 mg/kg were tolerated by rats without mortalities. The oral LD50 in rats is >500 mg/kg; in mice >2,500 mg/kg. The acute dermal toxicity dose of emodepside in rats is high; a dose of 2,000 mg/kg was tolerated without mortality.

Praziquantel has a wide margin of safety. In rats and mice, the oral $LD_{50}$ is at least 2 g/kg. An oral $LD_{50}$ could not be determined in dogs, as at doses greater than 200 mg/kg, the drug induced vomiting. Parenteral doses of 50–100 mg/kg in cats caused transient ataxia and depression. Injected doses at 200 mg/kg were lethal in cats.

Kittens approximately 8 weeks of age were treated topically with the combination product up to 5X at 2 week intervals for treatments. Clinical signs of transient salivation and/or tremors were seen in a few animals in the 5X group, all of which were self-limiting.

Seven- to eight-month-old cats treated topically with the topical solution at 10X developed transient salivation, tremor, and lethargy.

Studies where the product was administered orally in cats have caused salivation, vomiting, anorexia, tremors, abnormal respirations, and ataxia. Adverse effects in all animals treated in these studies resolved without treatment.

### Drug Interactions
No drug interactions have been documented for this product, but emodepside is reportedly a substrate for P-glycoprotein. Use with other drugs that are P-glycoprotein substrates or inhibitors (*e.g.*, **ivermectin, erythromycin, prednisolone, cyclosporine**) could cause pharmacokinetic drug interactions.

### Doses
- **CATS:**

For labeled indications:

a) Minimum dose is 3 mg/kg emodepside & 12 mg/kg praziquantel applied to the skin on the back of the neck as a single topical dose. A second treatment should not be necessary. If re-infection occurs, the product can be re-applied after 30 days. (Label information; *Profender*®—Bayer)

### Monitoring
- Clinical efficacy

### Client Information
- Do not apply to broken skin or if hair coat is wet.
- Do not get in the cat's mouth or eyes or allow the cat to lick the application site for one hour. Oral exposure can cause salivation and vomiting; treatment at the base of the head will minimize the opportunity for ingestion while grooming.
- In households with multiple pets, keep animals separated to prevent licking of the application site.
- Not for human use. Keep out of reach of children. To prevent accidental ingestion of the product, children should not come in contact with the application site for 24 hours while the product is being absorbed. Pregnant women, or women who may become pregnant, should avoid direct contact with, or wear disposable gloves when applying, this product.

### Chemistry/Synonyms
Emodepside is an N-methylated 24-membered cyclooctadepsipeptide, consisting of four alternating residues of N-methyl-L-leucine, two residues of D-lactate, and two residues of D-phenylacetate.

Praziquantel occurs as a white to practically white, hygroscopic, bitter tasting, crystalline powder, either odorless or having a faint odor. It is very slightly soluble in water and freely soluble in alcohol.

Praziquantel may also be known as: EMBAY-8440, or praziquantelum.

### Storage/Stability
Store product at or below 25°C (77°F); do not allow to freeze.

### Dosage Forms/Regulatory Status
**VETERINARY-LABELED PRODUCTS:**

Emodepside (1.98% w/w; 21.4 mg/mL) and Praziquantel (7.94% w/w; 85.8 mg/mL) Topical Solution in 0.35 mL (cats 2.2–5.5 lb.), 0.7 mL (cats >5.5–11 lb.) & 1.12 mL (cats >11–17.6 lb.) tubes: *Profender*® (Bayer); (Rx) Approved for use on cats.

**HUMAN-LABELED PRODUCTS:** None

## ENALAPRIL MALEATE
## ENALAPRILAT

(e-***nal***-a-pril) Enacard®, Vasotec®

**ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITOR**

### Prescriber Highlights
- **Veterinary & human ACE inhibitor used primarily as a vasodilator in the treatment of heart failure or hypertension; may also be of benefit in the treatment of chronic renal failure or protein losing nephropathies**
- **Contraindications: hypersensitivity to ACE inhibitors**
- **Caution: pregnancy, renal insufficiency (doses may need to be reduced), patients with hyponatremia, coronary or cerebrovascular insufficiency, preexisting hematologic abnormalities or a collagen vascular disease (e.g., SLE)**
- **Adverse Effects: GI distress (anorexia, vomiting, diarrhea); Potentially: weakness, hypotension, renal dysfunction & hyperkalemia**

## Uses/Indications

The principle use of enalapril/enalaprilat in veterinary medicine at present is as a vasodilator in the treatment of heart failure. Recent studies have demonstrated that enalapril, particularly when used in conjunction with furosemide, does improve the quality of life in dogs with heart failure. It is not clear, however, whether it has any significant effect on survival times. It may also be of benefit in treating the effects associated with valvular heart disease (mitral regurgitation) and left to right shunts. It is being explored as adjunctive treatment in chronic renal failure and protein losing nephropathies.

While ACE inhibitors are a mainstay for treating hypertension in humans, they have not been particularly useful in treating hypertension in dogs or cats.

## Pharmacology/Actions

Enalapril is converted in the liver to the active compound enalaprilat. Enalaprilat prevents the formation of angiotensin-II (a potent vasoconstrictor) by competing with angiotensin-I for the enzyme angiotensin-converting enzyme (ACE). ACE has a much higher affinity for enalaprilat than for angiotensin-I. Because angiotensin-II concentrations are decreased, aldosterone secretion is reduced and plasma renin activity is increased.

The cardiovascular effects of enalaprilat in patients with CHF include: decreased total peripheral resistance, pulmonary vascular resistance, mean arterial and right atrial pressures, and pulmonary capillary wedge pressure, no change or decrease in heart rate, and increased cardiac index and output, stroke volume, and exercise tolerance. Renal blood flow can be increased with little change in hepatic blood flow. In animals with glomerular disease, ACE inhibitors probably decrease proteinuria and help to preserve renal function.

## Pharmacokinetics

Enalapril/enalaprilat has different pharmacokinetic properties than captopril in dogs. It has a slower onset of action (4–6 hours) but a longer duration of action (12–14 hours). In humans, enalapril is well absorbed after oral administration, but enalaprilat is not. Approximately 60% of an oral dose is bioavailable. Both enalapril and enalaprilat are distributed poorly into the CNS and are distributed into milk in trace amounts. Enalaprilat crosses the placenta. In humans, the half-life of enalapril is about 2 hours; enalaprilat about 11 hours. Half-lives are increased in patients with renal failure or severe CHF.

## Contraindications/Precautions/Warnings

Enalaprilat is contraindicated in patients who have demonstrated hypersensitivity to the ACE inhibitors. It should be used with caution and close supervision in patients with renal insufficiency and doses may need to be reduced.

Enalaprilat should also be used with caution in patients with hyponatremia or sodium depletion, coronary or cerebrovascular insufficiency, preexisting hematologic abnormalities, or a collagen vascular disease (*e.g.*, SLE). Patients with severe CHF should be monitored very closely upon initiation of therapy.

## Adverse Effects

Enalapril/enalaprilat's adverse effect profile in dogs is principally GI distress (anorexia, vomiting, diarrhea). Potentially, weakness, hypotension, renal dysfunction and hyperkalemia could occur. Because it lacks a sulfhydryl group (unlike captopril), there is less likelihood that immune-mediated reactions will occur, but rashes, neutropenia, and agranulocytosis have been reported in humans. In humans, ACE inhibitors commonly cause coughs, but this occurs rarely in dogs or cats.

## Reproductive/Nursing Safety

Enalapril crosses the placenta. High doses in rodents have caused decreased fetal weights and increases in fetal and maternal death rates; teratogenic effects have not been reported. In humans, the FDA categorizes this drug as *category **C** for use during pregnancy in the first trimester* (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*) In humans, the FDA categorizes this drug as *category **D** for use during pregnancy in second and third trimesters* (*There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.*)

Enalapril/enalaprilat is excreted into milk. Safe use during nursing cannot be assumed.

## Overdosage/Acute Toxicity

In dogs, a dose of 200 mg/kg was lethal, but 100 mg/kg was not. In overdose situations, the primary concern is hypotension; supportive treatment with volume expansion with normal saline is recommended to correct blood pressure. Because of the drug's long duration of action, prolonged monitoring and treatment may be required. Recent overdoses should be managed by using gut emptying protocols when warranted.

## Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving enalaprilat and may be of significance in veterinary patients:

- **ANTIDIABETIC AGENTS** (**insulin, oral agents**): Possible increased risk for hypoglycemia; enhanced monitoring recommended
- **DIURETICS** (*e.g.*, **furosemide, hydrochlorothiazide**): Potential for increased hypotensive effects; some veterinary clinicians recommend reducing furosemide doses (by 25–50%) when adding enalapril or benazepril to therapy in CHF.
- **DIURETICS, POTASSIUM-SPARING** (*e.g.*, **spironolactone, triamterene**): Increased hyperkalemic effects, enhanced monitoring of serum potassium recommended
- **HYPOTENSIVE AGENTS, OTHER**: Potential for increased hypotensive effect
- **LITHIUM**: Increased serum lithium levels possible; increased monitoring required
- **NSAIDS**: May reduce the anti-hypertensive or positive hemodynamic effects of enalapril; may increase risk for reduced renal function
- **POTASSIUM SUPPLEMENTS**: Increased risk for hyperkalemia

## Laboratory Considerations

- When using iodohippurate sodium $I^{123}/I^{134}$ or Technetium $Tc^{99}$ pententate **renal imaging** in patients with renal artery stenosis, ACE inhibitors may cause a reversible decrease in localization and excretion of these agents in the affected kidney which may lead to confusion in test interpretation.

## Doses

- **DOGS:**
  a) As a vasodilator in heart failure: 0.5 mg/kg PO twice daily (Kittleson 2000)
  b) For adjunctive treatment of heart failure: 0.5 mg/kg once daily initially with or without food. If response is inadequate increase to 0.5 mg/kg twice daily (Package Insert; *Enacard®*—Merial)

  For adjunctive treatment of glomerular disease:
  a) For adjunctive treatment of glomerular disease: 0.5 mg/kg PO q12–24h (Grauer and DiBartola 2000)

b) For adjunctive treatment of glomerular disease/proteinuria: 0.5 mg/kg PO once daily. If no reduction in proteinuria after 2–4 weeks, increase to twice daily. (Vaden 2003)

As an adjunctive treatment for ureteroliths:

a) 0.25–0.5 mg/kg PO q12–24h; may potentially reduce interstitial expansion and fibrosis. (Lulich 2006)

■ **CATS:**

As a vasodilator in heart failure:

a) Initially, 0.25 mg/kg q12–24h (DeLellis and Kittleson 1992)

b) 0.25–0.5 mg/kg (roughly 1.25–2.5 mg per cat) PO once a day (q24h) (Meurs 2006d)

c) 0.5 mg/kg PO once daily, twice daily if necessary (Ware and Keene 2000)

For proteinuria, hypertension in chronic kidney disease:

a) 0.25 mg/kg PO once daily to 0.5 mg/kg PO twice daily; rarely higher (Polzin 2006)

■ **FERRETS:**

For adjunctive therapy for heart failure:

a) 0.5 mg/kg PO once every other day (q48h) initially and may be increased to once a day if tolerated. Dissolve tablet(s) in distilled water and add a methylcellulose suspending agent (*e.g.*, *Ora-Plus*®) and cherry syrup for flavor. (Hoeffer 2000)

b) For dilative cardiomyopathy: 0.25–0.5 mg/kg PO once a day to every other day (Williams 2000)

■ **BIRDS:**

For adjunctive therapy for heart failure:

a) 1.25 mg/kg PO two to three times daily (Pees, Kuhring et al. 2006)

## Monitoring

- Clinical signs of CHF
- Serum electrolytes, creatinine, BUN, urine protein
- CBC with differential, periodic
- Blood pressure (if treating hypertension or clinical signs associated with hypotension arise)

## Client Information

- May be given with or without food
- Do not abruptly stop or reduce therapy without veterinarian's approval
- Contact veterinarian if vomiting or diarrhea persist or are severe or if animal's condition deteriorates

## Chemistry/Synonyms

Angiotensin-converting enzyme (ACE) inhibitors, enalapril maleate and enalaprilat are structurally related to captopril. Enalapril is a prodrug and is converted *in vivo* by the liver to enalaprilat. Enalapril maleate occurs as a white to off white crystalline powder. 25 mg are soluble in one mL of water. Enalaprilat occurs as a white to off white crystalline powder and is slightly soluble in water.

Enalapril maleate may also be known as: enalaprili maleas, and MK-421; many trade names are available. Enalaprilat may also be known as: enalaprilic acid, MK-422, *Enacard*®, *Glioten*®, *Lotrial*®, *Pres*®, *Renitec*®, *Reniten*®, *Vasotec*®, and *Xanef*®.

## Storage/Stability/Compatibility

The commercially available tablets should be stored at temperatures less than 30°C in tight containers. When stored properly, the tablets have an expiration date of 30 months after manufacture.

Enalaprilat injection should be stored at temperatures less than 30°C. After dilution with $D_5W$, normal saline, or $D_5$ in lactated Ringer's it is stable for up to 24 hours at room temperature. Enalaprilat has been documented to be physically **incompatible** with amphotericin B or phenytoin sodium. Many other medications have been noted to be compatible with enalaprilat at various concentrations. Compatibility is dependent upon factors such as pH, concentration, temperature and diluent used; consult specialized references or a hospital pharmacist for more specific information.

## Dosage Forms/Regulatory Status

**VETERINARY-LABELED PRODUCTS:**

Enalapril Maleate Tablets: 1 mg, 2.5 mg, 5 mg, 10 mg, & 20 mg; *Enacard*® (Merial); (Rx). Approved for use in dogs.

The ARCI (Racing Commissioners International) has designated this drug as a class 3 substance. See the appendix for more information.

**HUMAN-LABELED PRODUCTS:**

Enalapril Maleate Tablets: 2.5 mg, 5 mg, 10 mg & 20 mg; *Vasotec*® (Biovail); generic (Rx).

Enalaprilat Injection: (for IV use) equivalent to 1.25 mg/mL in 1 mL and 2 mL vials; generic; (Rx)

# ENOXAPARIN SODIUM

**(en-*ocks*-a-par-in) Lovenox®**

**ANTICOAGULANT**

## Prescriber Highlights

- **Low molecular weight (fractionated) heparin that may be useful for treatment or prophylaxis of thromboembolic disease**
- **Preferentially inhibits factor Xa & only minimally impacts thrombin & clotting time (TT or aPTT)**
- **Hemorrhage unlikely, but possible**
- **Must be given subcutaneously, potentially every 6 hours**
- **Expense may be an issue, particularly in large dogs or horses**

## Uses/Indications

Enoxaparin may be useful for prophylaxis or treatment of deep vein thrombosis or pulmonary embolus. Recent pharmacokinetic work in dogs and cats, raises questions whether the drug can be effectively and practically administered long-term. In humans, it is also indicated for prevention of ischemic complications associated with unstable angina/non Q-wave MI.

## Pharmacology/Actions

By binding to and accelerating antithrombin III, low molecular weight heparins (LMWHs) enhance the inhibition of factor Xa and thrombin. The potential advantage to using these products over standard (unfractionated) heparin is that they preferentially inhibit factor Xa; only minimally impacting thrombin and clotting times (TT or aPTT).

## Pharmacokinetics

In dogs after SC administration, enoxaparin has a shorter duration of anti-Xa activity than in humans and probably must be dosed more frequently.

Cats appear to have a much shorter duration of activity (anti-Xa) associated with LMWHs than do humans and to maintain a therapeutic target of anti-XA activity of 0.5–1 IU/mL requires 1.5 mg/kg SC q6h dosing of enoxaparin. (Alwood, Downend et al. 2007)