BENAZEPRIL HCL

(ben-*a*-za-pril) Fortekor®, Lotensin®

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITOR

Prescriber Highlights

- ACE inhibitor that may be useful for treating heart failure, hypertension, chronic renal failure & protein-losing glomerulonephropathies in dogs & cats
- Caution in patients with hyponatremia, coronary or cerebrovascular insufficiency, SLE, hematologic disorders
- GI disturbances most likely adverse effects, but hypotension, renal dysfunction, hyperkalemia possible
- Mildly fetotoxic at high dosages

Uses/Indications

Benazepril may be useful as a vasodilator in the treatment of heart failure and as an antihypertensive agent, particularly in dogs. Reasonable evidence exists that ACE-inhibitors increase survival (when compared to placebo) in dogs with dilated cardiomyopathy and mitral valve disease. Benazepril may be of benefit in treating the clinical signs associated with valvular heart disease and left to right shunts. ACE inhibitors may also be of benefit in the adjunctive treatment of chronic renal failure and for protein losing nephropathies.

In cats, benazepril (or enalapril) can be used for treating hypertension, adjunctive treatment of hypertrophic cardiomyopathy, and reducing protein loss associated with chronic renal failure.

Pharmacology/Actions

Benazepril is a prodrug and has little pharmacologic activity of its own. After being hydrolyzed in the liver to benazeprilat, the drug inhibits the conversion of angiotensin-I to angiotensin-II by inhibiting angiotensin-converting enzyme (ACE). Angiotensin-II acts both as a vasoconstrictor and stimulates production of aldosterone in the adrenal cortex. By blocking angiotensin-II formation, ACE inhibitors generally reduce blood pressure in hypertensive patients and vascular resistance in patients with congestive heart failure. When administered to dogs with heart failure at low dosages (0.1 mg/kg q12h), benazepril improved clinical signs, but did not significantly affect blood pressure (Wu and Juany 2006)

In cats with chronic renal failure, benazepril has been shown to reduce systemic arterial pressure and glomerular capillary pressure while increasing renal plasma flow and glomerular filtration rates. It may also help improve appetite.

Like enalapril and lisinopril, but not captopril, benazepril does not contain a sulfhydryl group. ACE inhibitors containing sulfhydryl groups (*e.g.*, captopril) may have a greater tendency towards causing immune-mediated reactions.

Pharmacokinetics

After oral dosing in healthy dogs, benazepril is rapidly absorbed and converted into the active metabolite benazeprilat with peak levels of benazeprilat occurring approximately 75 minutes after dosing. The elimination half-life of benazeprilat is approximately 3.5 hours in healthy dogs.

In cats, inhibition of ACE is long-lasting (half-life of 16–23 hours), despite relatively quick elimination of free benazeprilat, due to high affinity of benazeprilat to ACE. Because enalaprilat exhibits nonlinear binding of benazeprilat to ACE, doses greater than 0.25 mg/kg PO produced only small incremental increases in peak effect or duration of ACE inhibition. (King, Maurer et al. 2003)

In humans, approximately 37% of an oral dose is absorbed after oral dosing and food apparently does not affect the extent of absorption. About 95% of the parent drug and active metabolite are bound to serum proteins. Benazepril and benazeprilat are primarily eliminated via the kidneys and mild to moderate renal dysfunction apparently does not significantly alter elimination as biliary clearance may compensate somewhat for reductions in renal clearances. Hepatic dysfunction or age does not appreciably alter benazeprilat levels.

Contraindications/Precautions/Warnings

Benazepril is contraindicated in patients who have demonstrated hypersensitivity to the ACE inhibitors.

ACE inhibitors should 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

Benazepril's adverse effect profile in dogs is not well described, but other ACE inhibitors effects in dogs usually center around GI distress (anorexia, vomiting, diarrhea). Potentially, 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 healthy cats given mild overdoses (2 mg/kg PO once daily for 52 weeks), only increased food consumption and weight were noted.

Reproductive/Nursing Safety

Benazepril apparently crosses the placenta. High doses of ACE inhibitors in rodents have caused decreased fetal weights and increases in fetal and maternal death rates; no teratogenic effects have been reported to date, but use during pregnancy should occur only when the potential benefits of therapy outweigh the risks to the offspring. In humans, the FDA categorizes this drug as category ***C*** for use during the first trimester of pregnancy (*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.*) During the second and third trimesters, the FDA categorizes this drug as category ***D*** for use during pregnancy (*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.*)

Benazepril is distributed into milk in very small amounts.

Overdosage/Acute Toxicity

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 massive overdoses should be managed using gut-emptying protocols as appropriate.

Drug Interactions

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

- **ASPIRIN**: Aspirin may potentially negate the decrease in systemic vascular resistance induced by ACE inhibitors; however, one study in dogs using low-dose aspirin, the hemodynamic effects of enalaprilat (active metabolite of enalapril, a related drug) were not affected

- **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 for heart failure
- **DIURETICS, POTASSIUM-SPARING** (*e.g.,* **spironolactone, triamterene**): Increased hyperkalemic effects, enhanced monitoring of serum potassium
- **LITHIUM**: Increased serum lithium levels possible; increased monitoring required
- **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:**

For adjunctive treatment of heart failure:

a) 0.25–0.5 mg/kg PO once daily (Miller and Tilley 1995); (Trepanier 1999), (Kittleson 2007)

b) 0.25–0.5 mg/kg PO once to twice daily (Ware 1997)

For adjunctive treatment of hypertension:

a) 0.25 mg/kg PO q12h (Brown and Henik 2000)

b) 0.25–0.5 mg/kg q12–24h; Co-administration with a calcium channel antagonist may lower blood pressure when monotherapy is not sufficient. In diabetic dogs, an ACE inhibitor may block adverse effects of calcium channel antagonists. (Brown 2003)

c) For hypertension associated with protein-losing renal disease: 0.5 mg/kg PO once daily (q24h) Response may be variable in dogs with hypertension secondary to other diseases; ACE inhibitors are usually well tolerated and can be tried in non-emergency hypertension. (Stepian 2006a)

- **CATS:**

For adjunctive treatment of heart failure:

a) 0.25–0.5 mg/kg PO once daily (Trepanier 1999), (Kittleson 2007)

b) For CHF or hypertension: 0.25–0.5 mg/kg PO once to twice daily (Atkins 2003b)

For adjunctive treatment of hypertension:

a) 0.5–1 mg/kg PO once daily (Sparkes 2003b)

b) 0.25–1 mg/kg PO once to twice daily. Because of their antiproteinuric effects, ACE inhibitors are the drugs of first choice to treat hypertension in animals with proteinuria. (Langston 2003)

c) 0.25–0.5 mg/kg PO once daily (q24h) (Stepian 2006a)

d) For proteinuria, hypertension associated with chronic kidney disease: 0.25–0.5 mg/kg PO once to twice daily (q12–24h); rarely higher (Polzin 2006)

Monitoring

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

Client Information

- Do not abruptly stop or reduce therapy without veterinarian's approval. Contact veterinarian if vomiting or diarrhea persist or is severe or if animal's condition deteriorates.

Chemistry/Synonyms

Benazepril HCl, an angiotensin converting enzyme inhibitor, occurs as white to off-white crystalline powder. It is soluble in water and ethanol. Benazepril does not contain a sulfhydryl group in its structure.

Benazepril may also be known as: CGS-14824A (benazepril or benazepril hydrochloride), *Benace®, Boncordin®, Briem®, Cibace®, Cibacen®, Cibacen®, Cibacene®, Fortekor®, Labopal®, Lotensin®, Lotrel®, Tensanil®,* or *Zinadril®.*

Storage/Stability/Compatibility

Benazepril tablets (and combination products) should be stored at temperatures less than 86°F (30°C) and protected from moisture. They should be dispensed in tight containers.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None in the USA

In the UK (and elsewhere): Benazepril Tablets: 2.5, 5, & 20 mg; *Fortekor®* (Novartis—UK); (POM-V) Labeled for use in cats for chronic renal insufficiency and for heart failure 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:

Benazepril HCl Tablets: 5 mg, 10 mg, 20 mg, & 40 mg; *Lotensin®* (Novartis); generic; (Rx)

Also available in fixed dose combination products containing amlodipine (*Lotrel®*) or hydrochlorothiazide (*Lotensin HCT®*)

BETAMETHASONE
BETAMETHASONE ACETATE
BETAMETHASONE SODIUM PHOSPHATE

(bet-ta-***meth***-a-sone) Celestone®

GLUCOCORTICOID

Note: For more information on the pharmacology of glucocorticoids refer to the monograph: Glucocorticoids, General information. For topical or otic use, see the Topical Dermatology & Otic sections in the appendix.

Prescriber Highlights

- Injectable (long-acting) & topical glucocorticoid
- Long acting; 25–40X more potent than hydrocortisone; no mineralocorticoid activity
- Goal is to use as much as is required & as little as possible for as short an amount of time as possible
- Primary adverse effects are "Cushingoid" in nature with sustained use
- Many potential drug & lab interactions when used systemically