The following is an English translation of the package insert for the drug sold in Japan (as of December 2012).

Chronic Heart Failure Drug for Dogs
Veterinary Drug
Prescription Legend Drug

Alacepril Tablet 6 mg
Alacepril Tablet 12.5 mg
Alacepril Tablet 25 mg

Alacepril Tablet is a mild, long-acting angiotensin-converting enzyme (ACE, kininase II) inhibitor synthesized and developed by Dainippon Sumitomo Pharma Co., Ltd. The active ingredient alacepril is converted in the body to deacetylalacepril, which is then further metabolized to captopril. Deacetylalacepril is effectively delivered to the arterial wall, where it directly inhibits peripheral sympathetic activity, resulting in vasodilation without modulation of the renin-angiotensin-aldosterone (RAA) system.
In addition, the active metabolite captopril inhibits ACE, thereby producing both arterial and venous dilation through modulation of the RAA system.
In an experimental chronic heart failure model in dogs, a single dose of 1 to 3 mg of alacepril was shown to result in sustained reduction of preload and afterload.
In clinical field studies, Alacepril Tablet was administered as a single agent or in combination with diuretic or cardiotonic agents to dogs with chronic heart failure from mitral regurgitation. The results showed that Alacepril Tablet more effectively inhibited the progression of heart disease and increased the exercise tolerance of animals when compared to treatment with conventional diuretic and cardiotonic agents alone, thereby demonstrating that Alacepril Tablet produces a significant improvement in symptoms.

■Composition
Alacepril Tablet 6 mg contains 6 mg of alacepril per tablet.
Alacepril Tablet 12.5 mg contains 12.5 mg of alacepril per tablet.
Alacepril Tablet 25 mg contains 25 mg of alacepril per tablet.

■Indications
Dogs: Improvement of symptoms associated with chronic heart failure from mitral regurgitation

■Dosage and Administration
The recommended dose in dogs is 1 to 3 mg of alacepril per kilogram of body weight per day, administered orally divided into 1 or 2 doses.

■Precautions
[General Precautions]
(1) Alacepril Tablet is a prescription legend drug to be used by or on the order of a licensed veterinarian.
(2) Alacepril Tablet should be used only for the purpose listed in the Indications section.
(3) Alacepril Tablet should be used only as indicated.

[User Precautions]
Consult a physician immediately in case of accidental ingestion by humans.

[Precautions for Dogs]

1. Restrictions

Do not use in pregnant or lactating dogs. Safety in pregnant and lactating dogs has not been established, and animal experiments (rats) have shown drug excretion in maternal milk. If use in lactating dogs cannot be avoided, prevent lactating.

2. Adverse Reactions

(1) Dizziness and other symptoms associated with the blood-pressure-lowering effect may develop. Dogs must be carefully monitored for 24 hours after the initial dose and dose escalation.
(2) Hematocrit, AST (GOT), ALT (GPT), BUN, creatinine, ALP and CLK may occasionally change.
(3) Anorexia and loss of vigor may be observed.
(4) Proteinuria may be occasionally observed.

3. Interactions

Do not use concomitantly with potassium-conserving diuretics.

4. Usage Precautions

(1) Appropriate supportive care should be provided (diuretic or cardiotonic agents), where necessary. The efficacy of Alacepril Tablet monotherapy in severe chronic heart failure has not been established.
(2) In dogs with hepatic and/or renal dysfunction and dogs with a history of hepatic and/or renal disease, start with a low dose. The dose should be increased gradually while carefully monitoring the animal's condition, if dose escalationis necessary.
(3) If prerenal azotemia is present, Alacepril Tablet and supportive care must be administered carefully while monitoring renal function. If azotemia (increased BUN and creatinine levels) develops during the administration of Alacepril Tablet, reduce the dose or discontinue use of diuretics first while carefully monitoring the animal's condition. If no improvement is noted, then reduce the dose or discontinue use of Alacepril Tablet and provide supportive care such as fluids.

[Storage Precautions]

(1) Keep out of the reach of children.
(2) Store Alacepril Tablet away from direct sunlight, high temperatures and high humidity.
(3) To avoid misuse and preserve quality, keep in the original package.

■Therapeutic Efficacy and Pharmacology

After oral administration, Alacepril Tablet is converted to deacetylalacepril and captopril, which reduce peripheral vascular resistance and preload and afterload by inhibiting the renin-angiotensin-aldosterone system.

1. Enzyme Inhibitory Effect

Although alacepril did not exhibit a marked enzyme (ACE, kininase II) inhibitory effect in vitro, in vivo, it exhibited a comparable inhibitory effect to the same amount of captopril by weight, but with a longer duration of effect.

2. Cardiac Effects in Dogs with Chronic Heart Failure

In an experimental canine model of chronic heart failure, a single administration of 1, 3 and 10 mg/kg of alacepril inhibited plasma ACE activity and produced sustained decreases in pulmonary artery wedge pressure (preload indicator) and total peripheral vascular resistance (afterload indicator). These changes were observed at doses of 1 mg/kg and above. The changes were comparable at the 3 mg/kg and 10 mg/kg doses.

3. Effect on Renal Function
Alacepril increased renal plasma flow, urine flow and urinary sodium excretion without significantly affecting creatinine clearance.

■***In Vivo* Pharmacokinetics**
1. Blood Concentration
After oral administration of 1.87 mg/kg of alacepril to six beagle dogs, the plasma concentration of free captopril reached a peak value of 337 ng/mL at approximately 0.5 hours, then decreased with a half-life of approximately one hour. The total plasma captopril concentration (free captopril plus mixed disulfides) reached a peak value of approximately 2.3 times the free captopril concentration at one hour, then decreased with a half-life of approximately five hours.

2. Distribution in Tissues
After administration of a single oral dose of [14C]alacepril to rats, the tissue radioactivity concentration peaked at one hour. The radioactivity concentration was highest in the kidneys (5.3 times the plasma concentration), followed by the liver (1.3 times the plasma concentration). The concentration was lower than the plasma concentration in all other tissues. The concentration in the brain was approximately 1/40 of the plasma concentration. Very little radioactivity was distributed to the central nervous system.
The tissue distribution of [14C]alacepril after repeat dosing was comparable to that after single dosing.

3. Metabolism
Alacepril is readily deacetylated to deacetylalacepril in the body after oral administration, then converted into free captopril by releasing phenylalanine. Deacetylalacepril exists in the circulating blood. Its protein conjugates efficiently transport captopril to the tissues. This mechanism is considered to contribute to the long-acting therapeutic effect of alacepril.

4. Excretion
After a single oral dose of [14C]alacepril to rats, 38 to 40% and 55 to 56% of the radioactivity dose was excreted respectively in the urine and feces by 96 hours.
After once daily repeat dosing for 10 days, the 24-hour urine and feces excretion rates were approximately constant at approximately 40% and 50% of the dose respectively, indicating that repeat dosing did not affect the excretion rates.

■**Toxicity**
1. Acute toxicity LD50 (mg/kg)

Animal Species/Sex \ Administration Route		Intraperitoneal	Subcutaneous	Oral
Mouse (ICR)	Male	2,921	>3,000	>5,000
	Female	3,031	>3,000	>5,000
Rat (SD)	Male	1,872	>3,000	>5,000
	Female	2,441	>3,000	>5,000
Dog (Beagle)	Male	-	-	>1,600
	Female	-	-	>1,600

2. Subacute and Chronic Toxicity
One-month subacute toxicity studies in rats and dogs showed anemia in rats at 300 mg/kg and dogs at 120 mg/kg. In addition, effects on the kidney (including increased BUN and renal tubule degeneration) and gastrointestinal system (diarrhea and soft stools) were observed in the high dose group.

In a six-month chronic toxicity study in rats, increased BUN was observed at 100 mg/kg and effects on urine and blood electrolytes were observed at 300 mg/kg. However, all of the events recovered after cessation of the drug.

3. Reproductive Effects

In a study of pre-pregnancy and early pregnancy administration in rats, no effects on the reproductive performance of dams or early fetal development were observed at 40 to 1000 mg/kg. In a study of administration during fetal organogenesis in rats, no embryolethality or teratogenicity was observed at 3000 mg/kg. In offspring, no effects other than mild inhibition of weight gain were observed at 3000 mg/kg. In a study of administration during fetal organogenesis in dogs, no embryolethality or teratogenicity was observed at 600 mg/kg. In a study of administration during the perinatal and lactation periods in rats, no effects were observed in offspring other than mild inhibition of weight gain and reduced number of implantation scars in animals that delivered F2 offspring at 1000 mg/kg.

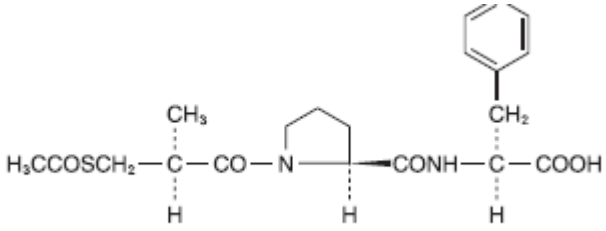
■Safety

No toxicity findings were observed on laboratory testing after 16 weeks of oral administration of 3, 10 and 30 mg/kg/day of alacepril to six-month old beagle dogs. The dose was therefore doubled and oral administration was continued through 52 weeks. The results showed a pattern of very mildly reduced systolic blood pressure at the low dose (3→6 mg/kg/day) and mildly reduced systolic blood pressure at the medium dose (10→20 mg/kg/day) and high dose (30→60 mg/kg/day). There were no other toxicologically significant findings.

■Description

1. Formulation

Alacepril Tablet 6 mg is a white, single-scored uncoated tablet.
Alacepril Tablet 12.5 mg is a white, double-scored uncoated tablet.
Alacepril Tablet 25 mg is a white, single-scored uncoated tablet.



2. Effective Ingredient

Generic name: Alacepril
Chemical name: 1-[(S)-3 -acetylthio - 2-methylpropanoyl]- L prolyl –L-phenylalanine
Molecular formula: $C_{20}H_{26}N_2O_5S$
Molecular weight: 406.50
Melting point: 153 to 157 °C
Description: Alacepril is a white, odorless or nearly odorless, crystal or crystalline powder with a slightly bitter taste. It is freely soluble in methanol, soluble in ethanol, sparingly soluble in acetone, slightly soluble in water and very slightly soluble in ether. It dissolves in sodium hydroxide reagent.

■Packaging

Alacepril Tablet 6 mg: 100 tablets (10 tablets × 10)
Alacepril Tablet 12.5 mg: 100 tablets (10 tablets × 10)
Alacepril Tablet 25 mg: 100 tablets (10 tablets × 10)

Marketing authorization holder
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