Vetmedin® (pimobendan) Chewable Tablets
Cardiac drug for oral use in dogs only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: Vetmedin (pimobendan) is supplied as oblong half-scored chewable tablets containing 1, 2.5, 5 or 10 mg pimobendan per tablet. Pimobendan, a benzimidazole-pyridazine-2-one derivative, is a non-sympathomimetic, non-glycoside inotropic drug with vasodilative properties. Pimobendan exerts a stimulatory myocardial effect by a dual mechanism of action: (1) an increase in calcium sensitivity of cardiac myofilaments and inhibition of phosphodiesterase (Type III). Pimobendan exhibits vasodilating activity by inhibiting phosphodiesterase III activity. The chemical name of pimobendan is 6-(4-β-D-thiophenyl-1H-benzimidazole-2-yl)-5-methyl-3H-2,3-dioxopyridazine. The structural formula of pimobendan is:

Indications: Vetmedin (pimobendan) is indicated for the management of the signs of mild, moderate, or severe (modified NYHA Class II, III, or IV) congestive heart failure in dogs due to atrioventricular valvular insufficiency (AVVI) or dilated cardiomyopathy (DCM). Vetmedin is indicated for use with concurrent therapy for congestive heart failure (e.g., furosemide, etc.) as appropriate on a case-by-case basis.

- A dog with modified New York Heart Association (NYHA) Class II heart failure has fatigue, shortness of breath, coughing, etc. apparent when ordinary exercise is exceeded.
- A dog with modified NYHA Class III heart failure is comfortable at rest, but exercise capacity is minimal.
- A dog with modified NYHA Class IV heart failure has no capacity for exercise and disabling clinical signs are present even at rest.

Dosage and Administration: Vetmedin should be administered orally at a total daily dose of 0.23 mg/kg (0.5 mg/kg body weight, using a suitable combination of whole or half tablets. The total daily dose should be divided into 2 portions that are not necessarily equal, and the portions should be administered approximately 12 hours apart (i.e., morning and evening). The tablets are scored and the calculated dosage should be provided to the nearest half tablet increment.

Contraindications: Vetmedin should not be given in cases of hypotrophic cardiomyopathy, aortic stenosis, or any other clinical condition where an augmentation of cardiac output is inappropriate due to anatomical or physiological reasons.

Warnings: Only for use in dogs with clinical evidence of heart failure. At 3 and 5 times the recommended dosage, administered over a 6-month period of time, pimobendan caused an exaggerated hemodynamic response in the normal dog heart, which was associated with cardiac pathology (See Animal Safety).

Human Warnings: Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans.

Precautions: The safety of Vetmedin has not been established in dogs with asymptomatic heart disease or in heart failure caused by etiologies other than AVVI or DCM. The safe use of Vetmedin has not been evaluated in dogs younger than 6 months of age, dogs with congenital heart defects, dogs with diabetes mellitus or other serious metabolic diseases, dogs used for breeding, or pregnant or lactating bitches.

Adverse Reactions: Clinical findings/adverse reactions were recorded in a 56-day field study with congestive heart failure (CHF) due to AVVI (256 dogs) or DCM (99 dogs). Dogs were treated with either Vetmedin (175 dogs) or the active control enalapril maleate (180 dogs). Dogs in both treatment groups received additional background cardiac therapy (See above).

Adverse reactions/new clinical findings were consistent with those reported in the 56-day study, with the following exception: One dog in the extended-use study developed acute cholestatic liver failure 140 days on Vetmedin and furosemide.

In foreign-post approval drug reporting, the following additional suspected adverse reactions were reported in dogs treated with a capsule formulation of Vetmedin: hemorrhage, petchxia, anemia, hyperglycemia, altered behavior, euthymia, pancreatitis, and diabetes mellitus.

To report suspected adverse reactions, to obtain a Material Safety Data Sheet, or for technical assistance call 1-800-367-7991.

Clinical Pharmacology: Pimobendan is oxadiazole demethylated to a pharmacologically active metabolite which is then conjugated with sulfite or glucuronic acid and excreted mainly via feces. The mean extent of protein binding of pimobendan and the active metabolite in dog plasma is >95%. Following a single oral administration of 0.25 mg/kg Vetmedin tablets the maximal mean ± 1 SD plasma concentrations (Cmax) of pimobendan and the active metabolite were 3.09 (0.70 mg/ml) and 3.61 (0.21) mg/ml, respectively. Individual dog Cmax values for pimobendan and the active metabolite were observed 1 to 4 hours post-dose (mean: 2.0 and 2.5 hours respectively). The total body clearance of pimobendan was approximately 90 mL/min/kg, and the terminal elimination half-lives of pimobendan and the active metabolite were approximately 0.5 hours and 12.0 hours respectively. Plasma levels of pimobendan and active metabolites were below quantifiable levels by 4 and 8 hours after oral administration, respectively. The steady-state volume of distribution of pimobendan is 1.6 L/kg indicating that the drug is readily distributed into tissues. Food decreased the bioavailability of an aqueous solution of pimobendan, but the effect of food on the absorption of pimobendan from Vetmedin tablets is unknown.

In normal dogs instrumented with left ventricular (LV) pressure transducers, pimobendan increased LV dp/dtmax (a measure of contractility of the heart) in a dose dependent manner between 0.1 and 0.5 mg/kg orally. The effect was still present 8 hours after dosing. There was a delay between peak blood levels of pimobendan and active metabolite and the maximum physiologic response (peak LV dp/dtmax). Blood levels of pimobendan and active metabolite began to drop before maximum contractility was seen. Repeated oral administration of pimobendan did not result in evidence of tachyphylaxis (decreased positive inotropic effect) or drug accumulation (increased positive inotropic effect). Laboratory studies indicate that the positive inotropic effect of pimobendan may be attenuated by the concurrent use of a β-adrenergic blocker or a calcium channel blocker.

Effectiveness: In a double-masked, multi-site, 56-day field study, 355 dogs with modified NYHA Class II, III, or IV CHF due to AVVI or DCM were randomly assigned to either the active control (enalapril maleate) or the Vetmedin (pimobendan) treatment group. Of the animals enrolled, 51% were male and 49% were female; 72% were diagnosed with AVVI and 28% were diagnosed with DCM. 34% had Class II, 47% had Class III, and 19% had Class IV CHF. Dogs ranged in age and weight from 0.25 kg and 2 years to 12 years and 151 kg respectively. The most common breed were mixed breed, Doberman Pinscher, Cocksh-Spaniel, Miniature/Toy Poodle, Maltese, Chihuahua, Miniature Schnauzer, Dachshund, and Cavalier King Charles Spaniel. The 180 dogs (130 AVVI, 50 DCM) in the active control group received enalapril maleate (0.5 mg/kg once or twice daily), and all but 2 received furosemide. Per protocol, all dogs with DCM in the active control group received digoxin. The 175 dogs (126 AVVI, 49 DCM) in the Vetmedin group received pimobendan (0.5 mg/kg/day divided into 2 portions that were not necessarily equal, and the portions were administered approximately 12 hours apart), and all but 4 received furosemide. Digoxin was optional for treating supraventricular tachycardia in either treatment group, as was the addition of a β-adrenergic blocker if digoxin was ineffective in controlling heart rate. After initial treatment at the clinic on Day 1, dog owners were to administer the assigned product and concurrent medications for up to 56 days.

The determination of effectiveness (treatment success) for each case was based on improvement in at least 2 of the following 2 domains: (1) exercise intolerance (modified NYHA classification, pimobendan vs. enalapril) and (2) the investigator’s overall clinical effectiveness score (based on physical examination, radiography, electrocardiography, and clinical pathology). Treatment success was defined as the area under the curve of improvement in 2 domains compared to the terminal values.

Adverse reactions/new clinical findings in the extended-use study were consistent with those reported in the 56-day study, with the following exception: One dog in the extended-use study developed acute cholestatic liver failure 140 days on Vetmedin and furosemide.

Table 1: CHF Death and New Arrhythmias in the 56-Day Field Study

Table 2: Effectiveness Results for the 56-Day Field Study

At the end of the 56-day study, the dogs in the Vetmedin group were enrolled in an unmasked field study to monitor safety under extended use, without restrictions on concurrent medications.
Vetmedin was used safely in dogs concurrently receiving furosemide, digoxin, enalapril, atenolol, spironolactone, nitroglycerin, hydralazine, diltiazem, antiparasitic products (including heartworm preventives), antibiotics (amoxicillin, cephalaxin, amoxicillin-clavulanate, fluoroquinolones), topical ophthalmic and otic products, famotidine, theophylline, levothyroxine sodium, diphtheria toxoid, hydrocortisone, metoclopramide, and butorphanol, and in dogs on sodium-restricted diets.

Palatability: In a laboratory study, the palatability of Vetmedin was evaluated in 20 adult female Beagle dogs offered doses twice daily for 14 days. Ninety percent (18 of 20 dogs) voluntarily consumed more than 70% of the 28 tablets offered. Including dogs that consumed only 4 and 7% of the tablets offered, the average voluntary consumption was 84.2%.

Animal Safety: In a laboratory study, Vetmedin chewable tablets were administered to 6 healthy Beagles per treatment group at 0 (control), 1, 3, and 5 times the recommended dosage for 6 months. See Table 3 for cardiac pathology results. The cardiac pathology/histopathology noted in the 3X and 5X dose groups is typical of positive inotropic and vasodilator drug toxicity in normal dog hearts, and is associated with exaggerated hemodynamic responses to these drugs. None of the dogs developed signs of heart failure and there was no mortality.

Table 3: Incidence of Cardiac Pathology/Histopathology in the Six-month Safety Study

<table>
<thead>
<tr>
<th>Severe left ventricular hypertrophy with multifocal subendocardial ischemic lesions</th>
<th>One 3X and two 5X dogs</th>
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</thead>
<tbody>
<tr>
<td>Moderate to marked myxomatous thickening of the mitral valves</td>
<td>Three 5X dogs</td>
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<tr>
<td>Myxomatous thickening of the chordae tendineae</td>
<td>One 3X and two 5X dogs</td>
</tr>
<tr>
<td>Endocardial thickening of the left ventricular outflow tract</td>
<td>One 3X, two 3X, and two 5X dogs</td>
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<tr>
<td>Left atrial endocardial thickening (jet lesions) in 2 of the dogs that developed murmurs of mitral valve insufficiency</td>
<td>One 3X and one 5X dog</td>
</tr>
<tr>
<td>Granulomatous inflammatory lesion in the right atrial myocardium</td>
<td>One 3X dog</td>
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</tbody>
</table>

Murmurs of mitral valve insufficiency were detected in one 3X (Day 65) and two 5X dogs (Days 135 and 163). These murmurs (grades II-III of VI) were not associated with clinical signs.

Indirect blood pressure was unaffected by Vetmedin at the label dose (1X). Mean diastolic blood pressure was decreased in the 3X group (76 mmHg) compared to the control group (82 mmHg). Mean systolic blood pressure was decreased in the 5X group (124 mmHg) compared to the control group (126 mmHg). None of the dogs had clinical signs of hypotension.

On 24-hour Holter monitoring, mean heart rate was increased in the 5X group (101 beats/min) compared to the control group (94 beats/min). None of the dogs had clinical signs associated with these electrocardiogram changes.

Treatment was associated with small differences in mean platelet counts (decreased in the 3X and 1X groups), potassium (increased in the 5X group), glucose (decreased in the 1X and 3X groups), and maximum blood glucose in glucose curves (increased in the 5X group). All individual values for these variables were within the normal range. Three 1X and one 5X group dogs had mild elevations of alkaline phosphatase (less than two times normal).

Loose stools and vomiting were infrequent and self-limiting.

Storage Information: Store at 20° to 25°C (68° to 77°F), excursions permitted between 15° and 30°C (between 59° and 86°F).

How Supplied: Vetmedin® (pimobendan) Chewable Tablets: Available as 1.25, 2.5, 5, and 10 mg oblong half-scored chewable tablets - 50 tablets per bottle.

NDC 0010-4480-01 - 1.25 mg - 50 tablets
NDC 0010-4482-01 - 2.5 mg - 50 tablets
NDC 0010-4481-01 - 5 mg - 50 tablets
NDC 0010-4479-01 - 10 mg - 50 tablets

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Mexico City, Mexico

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