Pimobendan is a benzimidazole-pyridazinone derivative, labeled for use in dogs to manage congestive heart failure (CHF) resulting from dilated cardiomyopathy (DCM) or degenerative mitral valve disease (DMVD) in the United States. On the basis of its positive inotropic effects combined with arteriovenous dilation, it is classified as an inodilator.\(^1\)

In this article, we provide relevant information about the pharmacology of pimobendan based on a review of the literature providing evidence to support its use for a variety of indications. As additional research is published, the indications and recommended uses for pimobendan continue to evolve.

**FORMULATION AND DOSING**

Pimobendan is available as Vetmedin (vetmedin.com) in oblong, half-scored chewable tablets (1.25 mg, 2.5 mg, 5 mg, or 10 mg). Because the stability and efficacy of the drug in suspension are unknown, reformulating as an oral suspension should be avoided. In some countries outside of the United States, an intravenous preparation is available.

For dogs, the labeled dosage recommendation for pimobendan is 0.25 to 0.3 mg/kg PO q12h. The total daily dose can be administered in 2 unequal portions by using whole or half tablets.

For initial use, especially if a more rapid onset of action is desired, the tablets should be administered on an empty stomach; however, for more chronic use, they can be administered with food. In dogs and cats, the oral preparation is rapidly absorbed; peak effect occurs within 2 to 4 hours in dogs and 0.9 hours in cats.\(^1,2\)

**MECHANISMS OF ACTION**

**Increased Cardiac Contractility**

The positive inotropic effects of pimobendan are mediated through a combination of 1) increased cyclic adenosine monophosphate mediated by phosphodiesterase III (PDEIII) inhibition, and 2) sensitization of the cardiac contractile apparatus to intracellular calcium. Calcium sensitization results in a positive inotropic effect without increasing myocardial oxygen demand.

**Vasodilation**

Balanced vasodilatory effects are mediated predominately through PDEIII inhibition in arterial
and venous vascular smooth muscle. Additional endothelial-mediated vasodilation mechanisms may also contribute to this action and may be linked to the medication’s beneficial effect in the treatment of pulmonary hypertension.3

Anticoagulation and Other Properties

In platelets, PDEIII inhibition mediates antithrombotic properties, leading to reduced platelet aggregation. This effect has been investigated in other pyridazinone-based compounds as well as pimobendan.4 In a study of healthy dogs, pimobendan mildly inhibited platelet aggregation but at a concentration well above a clinically relevant dose.5 In mice in heart failure, pimobendan reduced some of the adverse cytokine concentrations.6

INDICATIONS

Pimobendan is used to treat preclinical and clinical DCM and DMVD (TABLE 1, BOX 1).

Left-Sided and Right-Sided CHF

CHF can develop for reasons other than DMVD or DCM. To justify initiation of pimobendan when the underlying CHF etiology is unclear or for symptomatic patients when standard therapy has failed (stage D) (TABLE 1), echocardiography is typically indicated. When in doubt, consultation with a cardiologist is recommended.

Other Indications

- Congenital heart disease with volume overload (e.g., patent ductus arteriosus, ventricular septal defect, atrial septal defect, mitral or tricuspid valve dysplasia) complicated by CHF.
- Congenital heart disease characterized by obstruction (e.g., subaortic stenosis, pulmonic stenosis) with secondary myocardial failure in a patient with symptoms refractory to standard therapy. For these cases, we strongly recommend consultation with a cardiologist before initiation of pimobendan.

Pimobendan seems to be safe and well tolerated. Reported adverse effects are relatively rare and are typically limited to gastrointestinal upset associated with the chewable tablets.
Pulmonary hypertension unrelated to DMVD, resulting in right-sided CHF (ascites) refractory to standard therapy (i.e., cor pulmonale, advanced heartworm disease, pulmonary thromboembolism). For these patients, pimobendan can be added to other therapies; however, we recommend first consulting a cardiologist.

CONTRAINDICATION
When ascites is the result of pericardial effusion that requires pericardiocentesis, use of pimobendan is not recommended.

PRECAUTIONS
Pimobendan seems to be safe and well tolerated. Reported adverse effects are relatively rare and are typically limited to gastrointestinal upset associated...
with the chewable tablets. Significant overdose has reportedly resulted in pimobendan toxicity, manifested as severe tachycardia and mild changes in blood pressure.\footnote{19}

Pimobendan should be used cautiously in patients with an outflow tract obstruction, which includes the following:

- Subaortic stenosis
- Pulmonic stenosis
- Systolic anterior motion of the mitral valve
- Asymmetric septal hypertrophy

If pimobendan is given to a patient with outflow tract obstruction or low systemic blood pressure, to ensure that it is well tolerated, you should reassess both blood pressure and heart rate approximately 1 to 2 hours after the first dose of pimobendan is given.

**Interactions with other drugs** have not been reported.

**TAKE-HOME POINTS**

- Pimobendan is an inodilator labeled for use in dogs with CHF resulting from DCM or DMVD.
- Pimobendan is recommended for the treatment of DMVD stages B2 (that meet EPIC criteria), C, and D and DCM stages B2, C, and D.
- Pimobendan can be beneficial used alone or in combination with other cardiac drugs.
- Beneficial effects for dogs in stage B2 DMVD or DCM include prolongation of symptom-free and overall survival times.
- Beneficial effects for dogs in stages C/D DMVD or DCM include reduced clinical signs and heart size and increased survival times.
- Pimobendan should **not** be used in dogs with ascites resulting from pericardial effusion.

**CASE SCENARIOS**

**Case 1**

You are performing an annual wellness examination of a 7-year-old, 31-kg, spayed female Doberman pinscher. You auscultate a grade 2/6 systolic, left apical heart murmur and an arrhythmia. No clinical signs have been reported. The signalment and auscultation characteristics support a possible diagnosis of DCM. ECG (3 minute) and echocardiography are performed (**FIGURE 1**).

**Does this dog have preclinical DCM?** Yes, this dog has preclinical DCM (stage B2) on the basis of echocardiographic evidence of left ventricular dilation in systole of 4 cm (reference range 2.9 ± 0.3 cm) and diastole of 4.8 cm (reference range 3.8 ± 0.2 cm), low fractional shortening (16.6%; reference is >24%), left atrial dilation, and normal mitral valve morphology.\footnote{20} Mild mitral regurgitation was documented as a consequence of the left ventricular dilation. The ECG demonstrated a sinus arrhythmia with 1 ventricular premature contraction.

**FIGURE 1.** Dog with DCM. (A) Lead II ECG documenting sinus arrhythmia with a single ventricular premature contraction (25 mm/s; 10 mm/mV); (B) echocardiogram of the left atrium with the LA/Ao-2D; (C) echocardiogram of the short axis left ventricle M-mode with the left ventricular internal dimension in diastole (LVIDd) and in systole (LVIDs).
What should you do next? Consider further diagnostics, including thyroid assessment and a 24-hour ambulatory ECG (Holter examination). Hypothyroidism could be a contributing cause for the systolic dysfunction. Holter examination findings could better characterize the frequency and severity of the ventricular arrhythmias and help you determine if there is any need for antiarrhythmic therapy at this time.

Pimobendan added to heart failure therapy (furosemide and benazepril) improves clinical status, delays onset of refractory signs of heart failure, and increases survival times.10,11

No antiarrhythmic medication is indicated at this time because the dog is asymptomatic and showed only 1 ventricular premature contraction on a 3-minute ECG. Holter monitoring, whether performed now or in the future, may lead you to alter this decision.

Is pimobendan recommended for this dog? Yes, initiation of pimobendan is recommended on the basis of the PROTECT study results. In addition, initiation of an angiotensin-converting enzyme (ACE) inhibitor can be considered according to findings of a retrospective study of Doberman pinschers, which suggests that these drugs delay disease progression.21 However, before starting an ACE inhibitor, you should assess serum biochemistry.

Case 2

You are performing an annual wellness examination of a 9-year-old, 12-kg, spayed female Jack Russell terrier. You auscultate a grade 4/6 systolic, left apical heart murmur. No clinical signs are reported, and the signalment and murmur characteristics support a probable diagnosis of preclinical (stage B1 or B2) DMVD.

Thoracic radiography and echocardiography are performed to determine if the dog has cardiomegaly.
Is this dog a candidate for pimobendan therapy? Yes, initiating pimobendan therapy is recommended. This dog meets the EPIC criteria (VHS >10.5, L/Ao-2D ≥1.6, LVIDdN ≥1.7). The echocardiogram confirms DMVD: thick mitral valve leaflets and an eccentric jet of mitral regurgitation. The VHS is 10.9, and the LA/Ao-2D measured as depicted on FIGURE 2 is 2.1. The LVIDd is increased to 4.2 cm (reference range 2.8 to 4.0 cm),20 and the LVIDdN is 2.0 (FIGURE 2). TVP

References

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In the absence of an equally effective drug licensed for use in cats, pimobendan has been used in patients of this species. To download information about off-label use of pimobendan in cats, please visit TODAYSVETERINARYPRACTICE.COM