

Clopidogrel

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Clopidogrel, an oral antiplatelet medication in the thienopyridine drug class, is indicated in cats with or at risk for intracardiac thrombi development. It is also used in dogs with active thromboembolic disease or other prothrombic conditions.

CLINICAL APPLICATIONS

Clopidogrel is indicated in animals with documented thrombosis to limit further platelet aggregation and thrombi expansion.

- In cats, thrombi are most often observed on echocardiographic evaluation of the left auricular appendage or in the distal aorta following cardiogenic embolism.¹
- In dogs, arterial thrombosis has been associated with renal disease, corticosteroid administration, neoplasia, and heart disease.² Portal venous thrombosis has been associated with hepatic disease, neoplasia, immune and infectious diseases, and corticosteroid administration.³

Clopidogrel is often administered to dogs and cats with a perceived increased risk for thrombosis,

although few studies have evaluated the efficacy of this approach.^{4,5}

In cats, a total dose of 18.75 mg (one-quarter of a 75-mg tablet) PO once a day has been shown to reduce platelet aggregation and prolong oral mucosal bleeding time.⁶

- This dose should be administered clinically to cats, regardless of body weight.
- A prospective clinical trial comparing use of clopidogrel with use of aspirin in cats previously affected by arterial thromboembolism (ATE) showed a longer time to recurrent ATE in cats receiving clopidogrel (443 days) vs aspirin (192 days).⁴
 - Clopidogrel is therefore recommended as thromboembolic protection in cats found to be at risk for ATE.

In dogs, 1-2 mg/kg PO once a day for 3 days resulted in maximal platelet inhibition.⁷

- Alternatively, an oral loading dose of 10 mg/kg provided maximal platelet inhibition within 90 minutes.⁷
- A pilot study of 24 dogs with immune-mediated hemolytic anemia failed to show a difference in 90-day survival when

ATE = arterial thromboembolism

treated with clopidogrel alone ($n = 8$), aspirin alone ($n = 8$), or a combination of the two ($n = 8$).⁵

Combined administration of clopidogrel and aspirin can be used for dual antiplatelet inhibition, as each agent acts on different platelet receptors.⁸

- However, increased risk for GI side effects have been reported in humans receiving dual therapy and are likely to occur in animals as well.⁸

MECHANISM & SPECTRUM OF ACTION

As a thienopyridine derivative, clopidogrel irreversibly inhibits the P2Y₁₂ receptor on platelets.⁹

- The ligand for this receptor is adenosine diphosphate (ADP).
 - When bound, ADP leads to platelet activation and initiates thrombosis.⁹

The active metabolite of clopidogrel is produced by biotransformation of the prodrug by hepatic cytochrome P450 enzymes.¹⁰

- Pharmacodynamic differences in clinical efficacy exist in humans (related to genetic variants in cytochrome P450 activity).¹⁰
 - As preliminarily reported in dogs, experimental upregulation of the cytochrome P450 system with rifampin resulted in a 3.4-fold increase in platelet inhibition; downregulation with cimetidine resulted in a 1.3-fold reduction in platelet inhibition when either drug was given for 4 days before clopidogrel administration.¹¹
- Steady-state inhibition of platelet function requires 5 to 7 days of therapy.^{7,10}
 - A loading dose can be given for more rapid effect.^{7,10}

DRUG MONITORING & INTERACTIONS

Platelet function is challenging to assess, with variable results and poor correlation among methods.¹²

- In dogs, platelet function does not return to normal until ≈ 7 days after discontinuation.⁷
 - Similar results were reported in cats, in which normalization of platelet function occurred 7 days after drug cessation.⁶
 - This has clinical importance, as cessation of clopidogrel therapy should be considered several days before elective surgery. Cessation requires balanced consideration of the patient's thrombotic risk vs perceived bleeding risk from surgery.

Clinical studies and trials in humans have suggested that metabolic interaction between clopidogrel and omeprazole could possibly result in reduction of antiplatelet activity.

- In 2009, the FDA issued a warning that clopidogrel effectiveness may be reduced when taken with omeprazole.^{13,14}
 - Subsequent studies, however, found reduced bleeding risk when clopidogrel and aspirin were combined with omeprazole and no increased risk for cardiovascular events.¹⁵
- In a recent experimental study in dogs, concurrent administration of omeprazole and clopidogrel resulted in an increased plasma concentration of the inactive metabolite of clopidogrel but no difference in antiplatelet effects as compared with administration of clopidogrel alone.¹⁶
- The significance of an adverse clopidogrel–omeprazole interaction in dogs or cats is uncertain.

ADVERSE EVENTS

In the prospective FAT CAT study, 1 of 39 cats developed icterus and elevated liver enzyme activity 40 days after receiving clopidogrel; this 1 cat had the only adverse events reported.⁴

Anecdotally, the most common adverse event observed in cats has been hypersalivation related to drug bitterness after oral administration of quartered tablets.⁴

- Notably, when clopidogrel was administered in a gelatin capsule, no oral or gastric irritation was reported.⁴

No adverse events have been reported in dogs receiving clopidogrel.

In humans, bleeding, either GI or at the site of arterial puncture, has been the most common adverse event observed.¹⁷

- The incidence of major bleeding in human patients receiving clopidogrel was initially reported as 3.7%, as compared with 2.7% in the placebo group.¹⁷
- Anecdotally and in limited clinical trials, the risk for spontaneous bleeding in dogs and cats receiving clopidogrel appeared to be very low or nonexistent.^{4,5}

ADP = adenosine diphosphate

See page 110 for references.

Heartgard[®] Plus (ivermectin/pyrantel)

CHEWABLES

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS: For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of ascarids (*Toxocara canis*, *Toxascaris leonina*) and hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*, *Ancylostoma braziliense*).

DOSAGE: HEARTGARD[®] Plus (ivermectin/pyrantel) should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) of body weight. The recommended dosing schedule for prevention of canine heartworm disease and for the treatment and control of ascarids and hookworms is as follows:

Dog Weight	Chewables Per Month	Ivermectin Content	Pyrantel Content	Color Coding On Foil Backing and Carton
Up to 25 lb	1	68 mcg	57 mg	Blue
26 to 50 lb	1	136 mcg	114 mg	Green
51 to 100 lb	1	272 mcg	227 mg	Brown

HEARTGARD Plus is recommended for dogs 6 weeks of age and older.

For dogs over 100 lb use the appropriate combination of these chewables.

ADMINISTRATION: Remove only one chewable at a time from the foil-backed blister card. Return the card with the remaining chewables to its box to protect the product from light. Because most dogs find HEARTGARD Plus palatable, the product can be offered to the dog by hand. Alternatively, it may be added intact to a small amount of dog food. The chewable should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

HEARTGARD Plus should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive product in a heartworm disease preventive program, the first dose of HEARTGARD Plus must be given within a month (30 days) of the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. Therefore, for optimal performance, the chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with HEARTGARD Plus and resumption of the recommended dosing regimen will minimize the opportunity for the development of adult heartworms.

Monthly treatment with HEARTGARD Plus also provides effective treatment and control of ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*). Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

EFFICACY: HEARTGARD Plus Chewables, given orally using the recommended dose and regimen, are effective against the tissue larval stage of *D. immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage. HEARTGARD Plus Chewables are also effective against canine ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*).

ACCEPTABILITY: In acceptability and field trials, HEARTGARD Plus was shown to be an acceptable oral dosage form that was consumed at first offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with HEARTGARD Plus which is not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with HEARTGARD Plus.

While some microfilariae may be killed by the ivermectin in HEARTGARD Plus at the recommended dose level, HEARTGARD Plus is not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

Keep this and all drugs out of the reach of children.

In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Store between 68°F - 77°F (20°C - 25°C). Excursions between 59°F - 86°F (15°C - 30°C) are permitted. Protect product from light.

ADVERSE REACTIONS: In clinical field trials with HEARTGARD Plus, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported following the use of HEARTGARD: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

SAFETY: HEARTGARD Plus has been shown to be bioequivalent to HEARTGARD, with respect to the bioavailability of ivermectin. The dose regimens of HEARTGARD Plus and HEARTGARD are the same with regard to ivermectin (6 mcg/kg). Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. HEARTGARD demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these trials and bioequivalency studies, support the safety of HEARTGARD products in dogs, including Collies, when used as recommended.

HEARTGARD Plus has shown a wide margin of safety at the recommended dose level in dogs, including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines and steroid preparations have been administered with HEARTGARD Plus in a heartworm disease prevention program.

In one trial, where some pups had parvovirus, there was a marginal reduction in efficacy against intestinal nematodes, possibly due to a change in intestinal transit time.

HOW SUPPLIED: HEARTGARD Plus is available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in convenient cartons of 6 and 12 chewables.

For customer service, please contact Merial at 1-888-637-4251.



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