Despite increasing bacterial resistance worldwide, penicillin-based antimicrobial agents remain one of the most important classes of antibiotics used in dogs, cats, and humans.¹

**PHARMACOLOGY & CLINICAL APPLICATIONS**

Ampicillin–sulbactam is a potentiated amino-penicillin that kills bacteria by blocking bacterial cell wall growth.²⁻⁴

- For details, see *Pharmacodynamics & Pharmacokinetics*.

This combination agent is usually reserved for treating bacterial infections known to produce β-lactamase.

- In humans, this agent is especially important in treating multidrug-resistant infections caused by *Acinetobacter baumannii*, an opportunistic gram-negative pathogen responsible for serious hospital-acquired infections.²⁻⁵

**In human medicine, increasing prevalence of bacterial resistance to ampicillin and amoxicillin-clavulanic acid has raised concerns.⁶⁻⁹**

- Use of ampicillin–sulbactam should be limited to cases in which a susceptible organism is strongly suspected or documented with susceptibility testing.
- When presumptive treatment is initiated, performing a culture is strongly recommended.
  - If the susceptibility of the isolated organism is resistant, ampicillin–sulbactam treatment should be discontinued.

**In veterinary medicine, extralabel use is likewise indicated only when a susceptible organism is strongly suspected or documented.**

- Routine extralabel use not recommended

In dogs and cats, ampicillin–sulbactam may be a rational empiric choice or presumptive therapy for the following clinical situations involving specific suspected pathogens (see *Spectrum of Activity*, page 44):

- Infections with penicillinase-producing anaerobes likely (eg, GI compromise)¹⁰⁻¹¹
Single therapy for penetrating skin injuries associated with cat bites, puncture wounds, and foreign bodies.

Combination therapy for systemic infection (eg, cholangitis, aspiration pneumonia, septicemia).

Susceptible infections during hospitalization, with de-escalation to amoxicillin–clavulanic acid because of its similar spectrum of activity or to amoxicillin when clinical need for β-lactamase inhibition has been ruled out.

Presumptive use in animals in which an infectious agent (eg, *Leptospira* spp) is suspected in association with acute kidney injury and/or hepatopathy.

Pending results of urine culture and leptospirosis testing (eg, urine PCR, serology)

• Clears leptospiremic phase of leptospirosis
  – Patients with confirmed leptospirosis should be transitioned to doxycycline.

In the United States, extralabel use of ampicillin–sulbactam in dogs and cats is limited to parenteral administration as extrapolated from human formulation.

Extralabel doses (based on ampicillin component) as recommended:

- For empiric therapy in critically ill dogs and cats: extralabel dosage, 15-30 mg/kg IV q6-8h
  – For systemic infections, use in combination with a parenteral drug with gram-negative activity (eg, aminoglycoside, fluoroquinolone).
- For infections susceptible to amoxicillin–clavulanic acid in patients unable to receive oral medication: extralabel dosage, 10-20 mg/kg IV or IM q8h
- Available as a 2:1 ratio of ampicillin to sulbactam for parenteral administration in vials as crystalline powder for reconstitution.
  - 1.5 g (1 g ampicillin sodium, 0.5 g sulbactam sodium)
  - 3 g (2 g ampicillin sodium, 1 g sulbactam sodium)
  - 15 g (10 g ampicillin sodium, 5 g sulbactam sodium)
- Reconstituted ampicillin–sulbactam stability is concentration- and temperature-dependent.
  - Concentration commonly used for IV administration is 30 mg/mL (20 mg/mL ampicillin, 10 mg/mL sulbactam; initially reconstituted in a small volume of sterile water to dissolve crystalline powder, followed by further dilution with 0.9% NaCl for final concentration for injection, which is stable at 4°C for 72 hours).
  - Administer IV slowly, over ≈15 to 20 minutes.

Aminopenicillins are eliminated by the kidneys (including a significant portion excreted via tubular secretion).

In some human patients with altered glomerular filtration rates due to renal azotemia, consideration should be given for dose adjustment.

Although no known data are available for veterinary patients, some animals with severe renal dysfunction may require dose reduction.

**PHARMACODYNAMICS & PHARMACOKINETICS**

Ampicillin–sulbactam is a potentiated (ie, β-lactamase inhibitor) aminopenicillin with bactericidal and time-dependent activity.

For antibacterial drugs with time-dependent activity, bactericidal activity depends on the duration of drug exposure above the minimum inhibitory concentration (MIC).

Because bacterial killing is time-dependent, clinical success, especially in the treatment of gram-negative infections, depends on retaining drug concentrations above the MICs during the entire dosing interval.

Ampicillin is a semisynthetic penicillin (ie, β-lactam antibiotic) that effectively kills bacteria by disrupting the bacterial cell wall.

Bacterial cell wall synthesis is inhibited through penicillin-binding proteins and by disrupting cell wall integrity via inhibition of the transpeptidation reaction responsible for bacterial cell wall cross-linking.

Sulbactam is a semisynthetic β-lactamase inhibitor that irreversibly binds and inactivates a variety of β-lactamases.

Used in combination with β-lactam antimicrobials to target bacterial strains that would otherwise be resistant to nonpotentiated β-lactam antibiotics.

Alone, sulbactam has weak antibacterial activity.

As an aminopenicillin, this combination has a short elimination half-life (healthy humans, 1 hour), resulting in need for frequent administration.

Overall, ampicillin–sulbactam is a relatively polar or hydrophilic drug combination.

In humans, drug concentrations are achieved in tissue (eg, bone, muscle, skin) and body fluids (eg, sputum, peritoneal fluid).
**SPECTRUM OF ACTIVITY**

- Susceptible gram-positive aerobes include *Staphylococcus* spp, *Streptococcus* spp, *Enterococcus faecalis*, and *Actinomyces* spp
  - Ineffective against methicillin-resistant *Staphylococcus* spp
- Susceptible gram-negative aerobes including β-lactamase-producing bacteria (ie, *Escherichia coli*, *Pasteurella* spp, *Klebsiella* spp, *Proteus* spp) and *Salmonella* spp
- Ineffective against bacterial strains containing type 1 β-lactamases, including *Citrobacter* spp, *Enterobacter* spp, *Serratia* spp, and *Pseudomonas* spp
- Also considered ineffective against *Pseudomonas aeruginosa* because of drug impermeability or drug efflux

**ADVERSE EVENTS & PRECAUTIONS**

**Adverse reactions include**

- Thrombophlebitis or allergic reactions (IV)
- Seizures (rapid IV infusion)
- Pain at injection site (IM)

**Other possible side effects include vomiting and diarrhea.**

- Hepatocellular cholestasis has been reported in association with administration of ampicillin–sulbactam in humans; this has not been reported in veterinary patients.
- Pregnancy and lactation
  - Penicillins are known to cross the placenta; however, ampicillin has been suggested as probably safe (class A) during pregnancy in dogs and cats, based on lack of toxicity or teratogenicity identified in other species.
  - Little is known about the safety of sulbactam during pregnancy and whether it crosses the placenta.
  - Breast milk concentrations of ampicillin and sulbactam are considered low, and both antimicrobial agents are considered compatible with breastfeeding in humans.

**References**

17. Roy J, Messier S, Labrecque O, Cox WR. Clinical and in vitro efficacy of...


**LOOK FOR THESE ARTICLES IN FUTURE ISSUES**

- Losartan
- Refractory Seizures
- Zonisamide
- Diarrhea in a Dog with Diabetes Mellitus

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**HEARTGARD Plus**

**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, Toxocara leonina) and hookworms (Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma braziliense).

**DOSEAGE:** HEARTGARD Plus (ivermectin/pyrantel) should be administered only at monthly intervals at the recommended minimum dose level of 6 mg/kg of ivermectin per kilogram (0.27 mg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (0.27 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:

<table>
<thead>
<tr>
<th>Dog Weight</th>
<th>Chews Per Month</th>
<th>Ivermectin Content</th>
<th>Pyrantel Content</th>
<th>Color Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 25 lb</td>
<td>1</td>
<td>68 mcg</td>
<td>57 mcg</td>
<td>Blue</td>
</tr>
<tr>
<td>26 to 50 lb</td>
<td>1</td>
<td>118 mcg</td>
<td>114 mcg</td>
<td>Green</td>
</tr>
<tr>
<td>51 to 100 lb</td>
<td>1</td>
<td>227 mcg</td>
<td>227 mcg</td>
<td>Brown</td>
</tr>
</tbody>
</table>

HEARTGARD Plus is recommended for dogs 6 weeks of age and older. For dogs 10-15 lb use the appropriate combination of 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 first 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, refeeding 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 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 (A. caninum, 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**.

Start treatment as soon as possible after the dog has been diagnosed with heartworm infection. The minimum interval between administer ivermectin alone after treatment of some dogs that have circulating microfilariae.

**HEARTGARD Plus** which is not effective against adult *Toxocara* and *Toxocara leonina*. Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

Keep this and all dogs 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** and the Dog & Hand logo are registered trademarks of Merial. ©2016 Merial, Inc., Duluth, GA. All rights reserved. HED/6B/TRADE/01/17.

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