

# Ampicillin–Sulbactam

Katrina R. Viviano, DVM, PhD, DACVIM, DACVCP  
 University of Wisconsin–Madison

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

**PHARMACOLOGY & CLINICAL APPLICATIONS**  
**Ampicillin–sulbactam is a potentiated aminopenicillin that kills bacteria by blocking bacterial cell wall growth.**<sup>2-4</sup>

▶ 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.<sup>2,5</sup>

MIC = minimum inhibitory concentration  
 PCR = polymerase chain reaction

**In human medicine, increasing prevalence of bacterial resistance to ampicillin and amoxicillin–clavulanic acid has raised concerns.**<sup>6-9</sup>

- ▶ 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)<sup>10,11</sup>

- ▶ Single therapy for penetrating skin injuries associated with cat bites, puncture wounds, and foreign bodies<sup>12</sup>
- ▶ Combination therapy for systemic infection (eg, cholangitis, aspiration pneumonia, septicemia)<sup>13-16</sup>
- ▶ 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  $\beta$ -lactamase inhibition has been ruled out<sup>17,18</sup>
- ▶ Presumptive use in animals in which an infectious agent (eg, *Leptospira* spp) is suspected in association with acute kidney injury and/or hepatopathy<sup>19</sup>
  - 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<sup>3</sup>
  - For empiric therapy in critically ill dogs and cats: extralabel dosage, 15-30 mg/kg IV q6-8h<sup>3</sup>
    - 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<sup>3</sup>
- ▶ Available as a 2:1 ratio of ampicillin to sulbactam for parenteral administration in vials as crystalline powder for reconstitution<sup>20</sup>
  - 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.<sup>20</sup>
  - 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).<sup>20</sup>
  - Administer IV slowly, over  $\approx$ 15 to 20 minutes.

- Aminopenicillins are eliminated by the kidneys (including a significant portion excreted via tubular secretion).<sup>21</sup>
  - In some human patients with altered glomerular filtration rates due to renal azotemia, consideration should be given for dose adjustment.<sup>21,22</sup>
  - 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,  $\beta$ -lactamase inhibitor) aminopenicillin with bactericidal and time-dependent activity.<sup>23</sup>**

- ▶ 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,  $\beta$ -lactam antibiotic) that effectively kills bacteria by disrupting the bacterial cell wall.<sup>2-4</sup>**

- ▶ 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  $\beta$ -lactamase inhibitor that irreversibly binds and inactivates a variety of  $\beta$ -lactamases.<sup>2-4</sup>**

- ▶ Used in combination with  $\beta$ -lactam antimicrobials to target bacterial strains that would otherwise be resistant to nonpotentiated  $\beta$ -lactam antibiotics
- ▶ Alone, sulbactam has weak antibacterial activity.

**As an aminopenicillin, this combination has a short elimination half-life (healthy humans, 1 hour),<sup>21</sup> 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).<sup>1,5</sup>

## ADVERSE EVENTS & PRECAUTIONS

### Adverse reactions include<sup>3,4,12</sup>

- ▶ 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<sup>24,25</sup>; 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.<sup>26,27</sup>
  - 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.<sup>3</sup>

## SPECTRUM OF ACTIVITY<sup>3,4</sup>

- ▶ 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  $\beta$ -lactamase-producing bacteria (ie, *Escherichia coli*, *Pasteurella* spp, *Klebsiella* spp, *Proteus* spp) and *Salmonella* spp
- ▶ Ineffective against bacterial strains containing type 1  $\beta$ -lactamases, including *Citrobacter* spp, *Enterobacter* spp, *Serratia* spp, and *Pseudomonas* spp
- ▶ Also considered ineffective against *Pseudomonas aeruginosa* because of drug impermeability or drug efflux
- ▶ Susceptible anaerobes including *Clostridium* spp, *Bacteroides* spp, *Prevotella* spp, *Fusobacterium* spp, *Peptostreptococcus* spp, and *Propionibacterium* spp

**KATRINA R. VIVIANO**, DVM, PhD, DACVIM, DACVCP, is a clinical associate professor in the department of medical sciences at University of Wisconsin–Madison. Her clinical interests include immune-mediated diseases and toxicology; her research interests include investigation of the role of antioxidants in health and disease, along with strategies for optimizing antimicrobial therapy. Dr. Viviano earned her DVM from University of Wisconsin–Madison, then completed a small animal rotating internship at University of Minnesota and an internal medicine residency at University of Wisconsin–Madison.

## References

1. Lode HM. Rational antibiotic therapy and the position of ampicillin/sulbactam. *Int J Antimicrob Agents*. 2008;32(1):10-28.
2. Betrosian AP, Douzinas EE. Ampicillin–sulbactam: an update on the use of parenteral and oral forms in bacterial infections. *Expert Opin Drug Metab Toxicol*. 2009;5(9):1099-1112.
3. Plumb D. Amoxicillin sodium–sulbactam sodium. In: Plumb D, ed. *Plumb's Veterinary Drugs*, digital ed. Tulsa, OK: Brief Media; 2015; monograph peer reviewed October 2015. Accessed September 2016.
4. Riviere JE, Papich MG.  $\beta$ -lactam antibiotics: penicillins, cephalosporins, and related drugs. In: Riviere JE, Papich MG, eds. *Veterinary Pharmacology and Therapeutics*. 9th ed. Ames, IA: Wiley-Blackwell; 2009:865-876.
5. Toussaint KA, Gallagher JC.  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations: from then to now. *Ann Pharmacother*. 2015;49(1):86-98.
6. Beever L, Bond R, Graham PA, et al. Increasing antimicrobial resistance in clinical isolates of *Staphylococcus intermedius* group bacteria and emergence of MRSP in the UK. *Vet Rec*. 2015;176(7):172.
7. Boothe DM, Boothe HW. Antimicrobial considerations in the perioperative patient. *Vet Clin North Am Small Anim Pract*. 2015;45(3):585-608.
8. Kataoka Y, Umino Y, Ochi H, Harada K, Sawada T. Antimicrobial susceptibility of enterococcal species isolated from antibiotic-treated dogs and cats. *J Vet Med Sci*. 2014;76(10):1399-1402.
9. Thungrat K, Price SB, Carpenter DM, Boothe DM. Antimicrobial susceptibility patterns of clinical *Escherichia coli* isolates from dogs and cats in the United States: January 2008 through January 2013. *Vet Microbiol*. 2015;179(3-4):287-295.
10. Unterer S, Lechner E, Mueller RS, et al. Prospective study of bacteremia in acute diarrhea syndromes in dogs. *Vet Rec*. 2015;176(12):309.
11. Wiest R, Rath HC. Gastrointestinal disorders of the critically ill. Bacterial translocation in the gut. *Best Pract Res Clin Gastroenterol*. 2003;17(3):397-425.
12. Greene CE, Calpin J. Antimicrobial drug formulary: ampicillin sulbactam (appendix). In: Greene CE, ed. *Infectious Diseases of the Dog and Cat*. 4th ed. St Louis, MO: Saunders; 2012:1217.
13. Dear JD. Bacterial pneumonia in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2014;44(1):143-159.
14. Dickinson AE, Summers JF, Wignall J, Boag AK, Keir I. Impact of appropriate empirical antimicrobial therapy on outcome of dogs with septic peritonitis. *J Vet Emerg Crit Care (San Antonio)*. 2015;25(1):152-159.
15. Goggs RAN, Boag AK. Aspiration pneumonitis and pneumonia. In: Silverstein DC, Hopper K, eds. *Small Animal Critical Care Medicine*. 2nd ed. St Louis, MO: Saunders; 2015:130.
16. Wagner KA, Hartmann FA, Trepanier LA. Bacterial culture results from liver, gallbladder, or bile in 248 dogs and cats evaluated for hepatobiliary disease: 1998-2003. *J Vet Intern Med*. 2007;21(3):417-424.
17. Roy J, Messier S, Labrecque O, Cox WR. Clinical and in vitro efficacy of

amoxicillin against bacteria associated with feline skin wounds and abscesses. *Can Vet J.* 2007;48(6):607-611.

18. Tabah A, Cotta MO, Garnacho-Montero J, et al. A systematic review of the definitions, determinants, and clinical outcomes of antimicrobial de-escalation in the intensive care unit. *Clin Infect Dis.* 2016;62(8):1009-1017.
19. Greene CE, Sykes JE, Moore GE, Goldstein RE, Schultz RD. Leptospirosis. In: Greene CE, ed. *Infectious Diseases of the Dog and Cat.* 4th ed. St Louis, MO: Saunders; 2011:431-447.
20. AuroMedica Pharma, Dayton NJ; ampicillin and sulbactam for injection USP [package insert]; NDC# 55150-116-20, 55150-117-00, 5515-118-99. Updated 2014.
21. Adnan S, Paterson DL, Lipman J, Roberts JA. Ampicillin/sulbactam: its potential use in treating infections in critically ill patients. *Int J Antimicrob Agents.* 2013;42(5):384-389.
22. Lorenzen JM, Broll M, Kaefer V, et al. Pharmacokinetics of ampicillin/sulbactam in critically ill patients with acute kidney injury undergoing extended dialysis. *Clin J Am Soc Nephrol.* 2012;7(3):385-390.
23. Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. *Infect Dis Clin North Am.* 2009;23(4):791-815, vii.
24. Köklü S, Köksal AS, Asil M, Kiyici H, Çoban S, Arhan M. Probable sulbactam/ampicillin-associated prolonged cholestasis. *Ann Pharmacother.* 2004;38:2055-2058.
25. See TT, Lee SP. Cholestasis associated with ampicillin/sulbactam therapy: a case report. *J Intern Med Taiwan.* 2006;17(2):87-90.
26. Root Kustritz MV. What drugs are unsafe to use during pregnancy in bitches? In: Root Kustritz MV. *Clinical Canine and Feline Reproduction: Evidence-Based Answers.* Ames, IA: Wiley-Blackwell; 2010:101-103.
27. Root Kustritz MV. What drugs are unsafe to use during pregnancy in queens? In: Root Kustritz MV. *Clinical Canine and Feline Reproduction: Evidence-Based Answers.* Ames, IA: Wiley-Blackwell; 2010:231-232.

## LOOK FOR THESE ARTICLES IN FUTURE ISSUES

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

# 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.



©HEARTGARD and the Dog & Hand logo are registered trademarks of Merial.  
©2015 Merial, Inc., Duluth, GA. All rights reserved. HGD16TRADEAD (01/17).

A SANOFI COMPANY